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Skin Cancer Prevention and Treatment

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LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Explain the common risk factors for skin cancer.
2. List the characteristics and stages of skin cancer.
3. Describe the recommended skin cancer screening and prevention strategies.
4. Recognize the current treatment options for early and late stages of skin cancer.
5. Describe the common adverse events of agents used to treat skin cancer.

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Skin Cancer Prevention and Treatment

Introduction

Most people love a good summer day at the beach or lounging by the pool. Unfortunately this could be doing damage to the body's largest organ – the skin! Melanoma is a form of cancer that develops from cells called melanocytes, located in the epidermis layer of the skin **(Figure 1, *page 14*).**[1] These cells produce melanin, which is the primary determinant of skin color.[1,2] In general, all people have the same number of melanocytes, however they differ by the type of genes in these cells which give instructions on how much melanin to produce. This concept results in different skin colors in different ethnic backgrounds. In the setting of cancer, the conversion from normal cell growth into cancerous cell growth results from numerous genetic mistakes. Specifically, genes that are responsible for regulating cell growth are deleted or genes that promote cells to grow faster and out of control can get expressed. Normal healthy cells have the capability to recognize when are they are old or damaged and induce cell death. Cancer cells unfortunately do not. They create more and more unnecessary cells, which results in the formation of a tumor. In melanoma, many of the tumors have a dark or brown appearance because they are still producing melanin.

Non-Melanoma Skin Cancer

Aside from melanoma, there are two other common skin cancers, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[1,2] Basal cell carcinoma is the most common occurring skin cancer and accounts for approximately 8 of 10 skin cancers with an estimated 2.8 million cases diagnosed annually.[3] Rarely fatal, BCC can be highly disfiguring if allowed to grow untreated.[1] Squamous cell carcinoma is the second most common skin cancer with an estimated 700,000 new cases and approximately 2,500 deaths each year.[1,3] Due to the positive prognosis with BCC and SCC and the lack of pharmacologic (medication) interventions, the focus of this module will be only on melanoma type skin cancer.

Melanoma Skin Cancer

Melanoma Incidence

Melanoma skin cancer is the fifth most common type of new cancer diagnosis for men and the seventh most common in women.[3] Consequently, 76,690 people will be diagnosed with melanoma and almost 10,000 deaths will be caused by melanoma in 2013. About half of all melanomas occur in people over the age of 50 years; however, even young people in their 20s can develop the disease. In fact, melanoma is one of the most commonly diagnosed cancers in people under the age of 30 years, which could possibly stem from the popularity of tanning beds among that age group.[2,4] Among different ethnic groups, Caucasians are thirty times more likely to develop melanoma in comparison to African Americans.[3]

Risk Factors

Melanoma is mostly curable if caught at an early stage.[2] Understanding the patient and environmental factors that predispose individuals to an increased risk is very important **(Figure 2).** Some risk factors for melanoma are visible from the exterior of the skin.[1,2,4] Moles are dense areas of melanin that begin to form during childhood and continue until around age 40 years. People who have many, large or atypical moles have an increased risk for melanoma. This risk is also increased in people with a fair complexion (light hair, green or blue eyes, freckled skin) as they produce less melanin which is important to protect against ultraviolet (UV) radiation. Exposure to UV by the sun or tanning beds is associated with the formation of melanoma. However, it seems that intermit-

Figure 2. Melanoma Risk Factors[4,6]
1. Excessive exposure to ultraviolet lights or sunburns
2. Family or past history of melanoma
3. Fair complexion (light hair, green or blue eyes, freckles)
4. Older age
5. Large or numerous moles
6. Immunosuppression

tent exposure to sun and frequent burns has a higher risk than chronic or low-grade exposure. The risk for skin cancer jumps 75% when people start using tanning beds before the age of 30 years. A family history of melanoma (familial melanoma) increases the risk of diagnosis and commonly the melanoma can develop at a much younger age than on average. Another population that has an increased incidence of melanoma is patients that are currently immunosuppressed either by medications, such as with organ transplant patients, or by disease, such as chronic lymphocytic leukemia patients. Lastly, with age the risk for skin cancer will also increase.

Melanoma Case Part 1:

Rebecca is a 47 year-old Caucasian female who loves to spend time outside being active and tending to her garden. She has been meaning to make an appointment with her dermatologist to have a skin exam performed. She is worried she is at an increased risk because her mother was diagnosed with melanoma when she was 50 years old and she gets frequent sun burns with her fair skin. Examine Rebecca's history and list if she has any factors that would increase her risk for melanoma.

Hair color: Red
Eye color: Green
Wt: 148 lbs
Ht: 5'6"
Skin: freckled with numerous moles

PMH: Hypertension

Risk Factors

1. _____
2. _____
3. _____
4. _____

Prevention/Screening

In order to prevent skin cancer there are simple guidelines to implement into daily life. Avoiding UV rays is key.[2] Parents should ensure their children have appropriate protection at all times as sunburns at an early age can increase the melanoma risk later on in life. To do this avoid direct sun between the hours of 10 a.m. and 4 p.m. When out in the sun, look for shade, especially in the middle of the day when the sun's rays are the strongest. One way to know this is if a person's shadow is shorter than they are, then the sun's rays are at the strongest. Also attempt to keep skin covered with protective clothing, guarding as much skin as possible. Long sleeves and pants are recommended. Clothing is available that has built in UV protection. To protect the head, wear a wide brimmed hat capable of shading the face, ears and neck.

It is highly recommended to use a broad-spectrum sunscreen and lip balm with a sun protection factor (SPF) of 15 or higher on a daily basis.[5] Broad-spectrum sunscreens protect against both ultraviolet A (UVA) and ultraviolet B (UVB) radiation from the sun. Ultraviolet A rays are responsible for chronic skin damage, such as wrinkles, and UVB rays cause more immediate damage like a sunburn. However, they both can cause cancer. Sun protection factor, or SPF, is the measurement of a sunscreen product's ability to prevent UVB damage to the skin. What the number actually means is if a person's unprotected skin starts turning red after 30 minutes in the sun, then using a sunscreen with SPF of 15 should prevent reddening 15 times longer – about 7 1/2 hours. Over the past few years there has been a large effort by the U.S. Food and Drug Administration (FDA) to regulate labeling and health claims on sunscreen products. As of January 2014, FDA new labeling rules apply to all sunscreen products. For a product to be called "broad-spectrum" it must protect from UVA and UVB. Only broad-spectrum products with SPF of at least 15 can claim they help protect against skin cancer and early skin aging. Terms such as "sunblock," "sweatproof," and "waterproof" can no longer be included on labels whereas "water-resistant" can be included only if the manufacturer states the clinically proven duration of swimming or sweating for which the product will provide protection. Sunglasses with 99% to 100% UVA and UVB protection are also recommended in order to provide optimal protection for the eyes and the surrounding skin. Avoid other sources of UV light such as tanning beds.

Detecting melanoma as early as possible is imperative and patients are often the most capable to screen themselves for skin cancer.[2,6] To do this, people should first become familiar with the difference between a normal and abnormal mole. The most common site for melanoma in men is the trunk and for women the legs. Physicians have developed easy to remember rules for evaluation of suspicious lesions represented by ABCDE **(Figure 3, *page 14*).** The letter "A" represents the development of an asymmetrical shape where one half or side of the mole/lesion does not match the other half or side. The letter "B" describes border irregularity when the edges of the mole appear

ragged or notched. The letter "C" focuses on the color of the mole. In melanoma, most commonly, the color of the mole is not the same throughout or there may be different shades of tan, brown or black and even sometimes patches of red, blue or white seen. The letter "D" represents the diameter of the mole, which may be irregular if wider than ¼ inch, which is comparable to the top of a pencil eraser. The letter "E" describes a mole with evolving properties whether it has changing size, shape, color or texture over the past few weeks or months. The American Cancer Society recommends performing a monthly skin self-exam with a full length mirror and a hand-held mirror or the help of a partner to review hard to reach or see spots like the back of thighs or scalp **(Figure 4).**[7] Patients should notify their physician immediately if any spots have changed or are concerning. Physicians should also screen patients at high risk for skin cancer, however, the U.S. Preventive Services Task Force stated that currently there is insufficient evidence to recommend for or against routine screening by primary care providers for all patients.[6]

Melanoma Case Part 2:

Rebecca visits her dermatologist who performs a skin exam. He says that everything looks good, but since she is at increased risk for melanoma he wants her to perform monthly self-skin exams looking for particular characteristics. Complete the spelling of the skin exam guidewords Rebecca's dermatologist would like her to keep in mind when she does her self-skin exam.

A _____

B _____

C _____

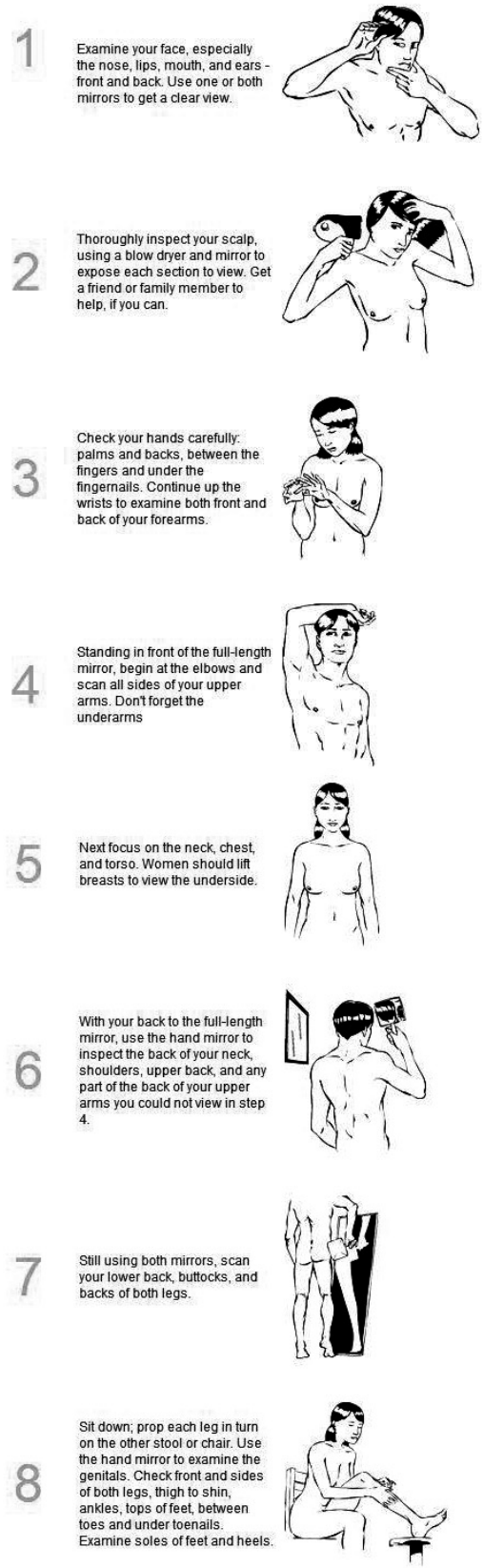
D _____

E _____

Clinical Manifestation

Melanoma most commonly look like pigmented lesions, however nodular or small knot-like lesions can arise.[2,6] Typically, people will notice a change in an existing lesion, mole, or freckle. In other situations there is a development of a new, unusual looking growth on the skin. These growths may be scaly or itch, or can look like spreading of the pigment from the mole/growth into surrounding skin. Other cases may have broken skin and bleeding of the lesion.

Figure 4. Skin Self-Examination



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Melanoma is a very dangerous cancer because it is more likely to spread throughout the body, especially the longer the time it is left undiagnosed.[2] When cancer affects other body parts than the initial site of growth it is called metastasis. Many biological events must happen to result in metastatic disease.[1] Initially the abnormal replication of cells is benign, not cancerous, with limited growth. When that growth increases we call the lesion premalignant. At this stage the tumor may regress and stay benign or progress into a radial growth stage with a widening diameter of tumor cells still within the epidermis. As the tumor cells overpopulate they can experience vertical growth downward into and across the basement membrane of the epidermis into the dermis **(Figure 5, *page 15*).** This is a crucial step in metastasis because once the tumor cells enter the dermis they come into contact with blood vessels and lymph nodes. These two structures provide ideal transportation vehicles for the malignant cells to reach other parts of the body. Most commonly, melanoma metastases are seen in the lungs, brain and lymph nodes.[1] Patients with metastasis at diagnosis can have symptoms specific to that organ such as shortness of breath, seizure, or a swollen lymph node.

There are five types of melanoma, each with distinct characteristics.[1,2] Superficial spreading melanoma is the most common type of melanoma and typically looks like a brown-black stain on the skin extending out from a mole or the appearance of a new mole on unaffected skin. This type of melanoma accounts for 70% of melanoma cases, usually seen in younger patients, and is associated with sun exposure. Similar to superficial spreading melanoma is lentigo maligna which also appears as a flat or mildly elevated dark area of discoloration. Lentigo maligna is most often diagnosed in the elderly after chronic sun exposure to areas such as the face, ears, arms and upper trunk. This type of melanoma is less common and accounts for around 5% of cases. Acral lentiginous melanoma is most common in African Americans and Asians appearing under nail beds, on the palms of the hands, and soles of the feet. These lesions are typically very dark brown or black and are more aggressive than lentigo maligna or superficial spreading melanoma. The most aggressive type of melanoma is nodular melanoma, due to the fact that it grows much faster and deeper than other melanomas. It accounts for 10-15% of melanomas and is recognized when it becomes a bump which is usually black in color but can occasionally appear blue, gray, white, brown, tan, red or skin tone. The most rare form of melanoma is mucosal melanoma.[8] Nearly half of these cases will stem from mucosal tissue of the head and neck region, however they also can appear in the female genital tract and ano-rectal region. This type of melanoma is not associated with UV exposure, and due to the lack of early and specific signs, is often diagnosed at late stages with a very poor prognosis.

Diagnosis

The first step to a diagnosis of melanoma is a surgical biopsy of the suspicious lesion.[9] The preferred type of biopsy would be what is called a full thickness excisional biopsy where the goal is to remove the entire lesion, leaving behind only normal-appearing skin. If this is not possible, an incisional or core-needle biopsy is conducted, which will remove a core of skin penetrating down through the entire depth of the lesion and into the subcutaneous tissue. Analysis of the biopsy will confirm the diagnosis. Providers will also conduct a complete family and medical history for all patients. Patients presenting with advanced disease may need additional tests including chest x-ray, lactate dehydrogenase levels and a computer tomography (CT) scan or magnetic resonance imaging (MRI) to evaluate the extent of disease.

Figure 6: Staging of Skin Cancer

American Joint Committe on Cancer (AJCC) Staging System[9]

Category:
- T: thickness of tumor, ulceration and mitotic rate
- N: lymph-node involvment
- M: metastasis to distant organs

Stage:
- 0: localized disease
- 1: localized disease ≥ 2 mm thickness
- 2: localized disease ≤ 4 mm thickness
- 3: nodal involvement no distant disease
- 4: advanced disease spread to distant organs

≥ greater than or equal to
≤ less than or equal to

Staging/Prognosis

The American Joint Committee on Cancer (AJCC) staging system for melanoma was updated in 2009 to more accurately reflect variables of prognostic significance in melanoma **(Figure 6).**[2,9] This system is comprised of three categories; T, N, M. Category T describes the vertical thickness, presence of ulceration, and how fast the cells are replicating in the lesion. Category N describes the lymph node involvement, with the number of lymph nodes, not the size, being the strongest predictor of outcome. Lastly, category M describes the presence of metastasis to distant organs. This category can be further defined by the number and site of metastasis. These three categories are then combined to assign a disease stage ranging from a scale of 0-4. Stage 0-2 signifies localized disease with differing lesion size; stage 3 signifies regional involvement yet no distant disease; and stage 4 recognizes the spread of disease to distant organs. At diagnosis, 84% of patients have localized or stage 0-2 disease, 8% present with regional disease or Stage 3 melanoma, and 4% are diagnosed with Stage 4 metastatic disease **(Figure 7, *page 15*).**[3] Based on this staging, localized or stage 0-2 patients have a five-year survival of 98%. Survival is reduced in regional disease to 61% and decreases to a mere 15% in patients with metastatic disease.

Treatment

Nonpharmacological Treatment of Melanoma

Surgery is the most common nonpharmacological (non-medication) treatment of melanoma.[6] During the surgery the surgeons will remove the tumor and a margin of tissue surrounding the tumor to ensure that no residual disease is missed. The size of the tissue margin depends on the thickness of the tumor **(Table 1).** If the tissue margins contain residual disease, repeat surgical excision is performed. Should the margins be disease-free, patients typically proceed to routine follow-up.

After surgery, patients with certain types of melanoma may require radiation therapy.[6] Radiation therapy is also used in patients with regional disease that meet specific criteria such as melanoma that has spread outside of the lymph nodes. In patients who cannot get their lymph nodes surgically removed, radiation therapy is used as symptom management to ease pain and other symptoms, rather than as a treatment option. Lastly, radiation therapy is used in patients with disease that has spread to the brain, soft tissue, or bone.

Pharmacological Treatment of Melanoma

Treatment of Early Stage (Non-Metastatic) Melanoma

For treatment of early stage, non-metastatic melanoma that cannot be removed with surgery or treated with radiation therapy, the treatment of choice is systemic therapy with either high dose interferon-a 2b (IFN- a 2b) or pegylated interferon.[2] In addition to the treatment of melanoma, IFN- a 2b, brand name Intron A, is also used to treat other types of cancers such as leukemia, lymphoma, AIDS-related Kaposi's sarcoma; and viral conditions such as chronic hepatitis C and chronic hepatitis B.[10] When used in melanoma, IFN- a 2b is given in two dosing phases: an induction phase during which it is given intravenously (IV) 5 days per week for 4 weeks, and then a maintenance phase where it is given subcutaneously three times weekly for 48 weeks. The dose for IFN- a 2b is based on body surface area, which is calculated using the patient's height and weight. The induction doses for IFN- a 2b are 20 million units/m^2/dose, while the maintenance dose is lower at 10 million units/m^2/dose. Pegylated interferon, brand names PegIntron and Sylatron, is only approved by the FDA to treat early stage melanoma.[11] Similar to IFN- a 2b, pegylated interferon is also administered in an induction phase and a maintenance phase. However, the dosing and schedule is different. The induction treatment is administered weekly for 8 weeks and the maintenance treatment is administered weekly for up to five years. The doses for pegylated interferon are calculated based solely on the patient's weight: induc-

Table 1. Surgical Margins Based on Tumor Thickness[9]

Tumor Thickness	Recommended Clinical Margins
In Situ	0.5-1.0 cm
≤ 1.0 mm	1.0 cm
1.01-2 mm	1 - 2 cm
2.01-4 mm	2.0 cm
>4 mm	2.0 cm

≤ less than or equal to
> greater than

tion doses are 6 mcg/kg/week, while the maintenance dose is cut in half at 3 mcg/kg/week. The main difference between pegylated interferon and IFN- a 2b is the frequency of dosing. This is due to the fact that the chemical structure of pegylated interferon has an extra molecule attached to it, allowing it to work in the body for an extended period of time with less frequent administration.[10,11] During the maintenance phase of both agents, patients can be trained to administer the subcutaneous injections themselves using a prefilled disposable syringe. It is important to rotate injection sites on the abdomen and thigh, while also administering each dose on the same day at the same time each week. Patients might find that night–time administration makes the medication easier to tolerate.

Though they have different chemical structures, pegylated interferon and IFN- a 2b both work to treat early stage melanoma through the same mechanism of action. Once in the body, these medications work by mimicking the body's natural interferon, a protein made in response to the presence of pathogens (disease causing agents) such as viruses, or in the case of melanoma, tumor cells.[10,11] Administration of these medications triggers a cascade of pathways which ultimately results in direct inhibition of tumor cell replication. Both IFN- a 2b and pegylated interferon have been shown to be effective in treating melanoma. Each agent demonstrated significantly increased relapse-free survival (RFS) when compared to patients undergoing observation, receiving no treatment.[11,12] The 5-year RFS of IFN- a 2b was 37%, compared to 26% in the observation group. Treatment with pegylated interferon showed a 4-year RFS of 45.6%, while the observation group resulted in a 38.9% 4-year RFS. Patients did experience side effects from treatment in both of these studies. Toxicities reported include: low blood cell counts, headache, dizziness, depression, fatigue, and body aches.[10-13]

The side effect of depression is one that may be of particular concern, as patients may be hesitant to undergo treatment with an agent for such prolonged periods (4-5 years) knowing depression may occur. However, it is important to note that the incidence of depression with these agents was highest at the beginning of therapy and patients reported an improvement in depression as therapy went on. All patients receiving IFN- a 2b and pegylated interferon should be monitored closely for any signs and symptoms of depression. Once diagnosed, proper management should be employed to lessen and control the patient's symptoms. Another common side effect of these medications is flu-like symptoms, including body aches, fever and fatigue. In order to prevent this, all patients must be premedicated with acetaminophen before each dose. Other toxicities include gastrointestinal effects such as anorexia, nausea, diarrhea, and taste alteration. Lastly, hair loss and rash are also seen in patients receiving IFN- a 2b or pegylated interferon.[10-13] Due to their similar side effect profile, the choice between treatment options may come down to convenience, insurance coverage or patient and provider preference.

Treatment of Late Stage (Metastatic) Melanoma Chemotherapy

While there are effective treatment options for early stage melanoma, treatment for late stage, or metastatic melanoma, has not been as successful. Historically, the preferred treatment recommendation from the National Comprehensive Cancer Network (NCCN), was to enter into a clinical trial.[9] Many of these trials investigated the use of chemotherapy, specifically dacarbazine (DTIC-Dome) and temozolomide (Temodar), with reported minimal success.[6,14-17]

Studies of dacarbazine and temozolomide have shown a 7-20% response rate (RR).[14-17] Those patients who achieved a response to treatment with dacarbazine or temozolomide experienced a median overall survival of approximately nine months. Temozolomide is a prodrug of dacarbazine, which means that it is converted to the same active metabolite as dacarbazine once it is inside of the body.[15] There are a number of ways prodrugs can be activated to their active drug form. In the case of temozolomide, it is spontaneously converted to the same active metabolite as dacarbazine in all body tissues. Therefore, because temozolomide is a prodrug of dacarbazine, both medications work the same way.[14,15] They are classified as alkylating agents, a group of medications that work by inhibiting DNA replication, RNA transcription, and nucleic acid formation which ultimately leads to cancer cell death **(Figure 8).** Both medications also have the same side effect profile, which includes: abnormal liver function tests, jaundice, nausea, vomiting, constipation, low blood cell counts, and fatigue.

Dacarbazine is the most widely studied agent for the treatment of metastatic melanoma and was FDA-approved for this indication in 1976.[14] It is available in multiple strength vials as powder for reconstitution. The powder should be reconstituted with sterile wa-

Figure 8. Mechanism of Action of Temozolomide[14,15]

ter for injection (SWFI) to a final concentration of 10 mg/mL. This reconstituted solution is further diluted in 250-1000mL of either 0.9% sodium chloride (NaCl) or 5% dextrose in water (D5W). In melanoma, dacarbazine is dosed based on body surface area (250 mg/m^2/dose) and given intravenously over 15-30 minutes on days 1-5 every three weeks. Prior to each dose of darcarbazine, patients receive multiple anti-emetics to prevent nausea and vomiting. The choice of anti-emetics is usually based on institutional drug formularies. Due to the fact that it is prepared intravenously, it is recommended that dacarbazine be administered by a chemotherapy certified nurse, which may not be convenient for all patients.

Temozolomide is most commonly used for brain cancers.[15] Of note, temozolomide is not FDA-approved for use in metastatic melanoma, but due to the fact that it works the same way as dacarbazine does, the NCCN includes temozolomide in its recommendations for the treatment of metastatic melanoma.[6] Temozolomide, like dacarbazine, is dosed based on body surface area (200 mg/m^2/day).[15] The dose of temozolomide should be rounded to accommodate the available dosage forms: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules. One thing to pay close attention to is the unique dosing schedule of temozolomide. It is given for the first five days of a 28-day cycle, which is similar to dacarbazine. However, because it is an oral medication, it is often dispensed for patients to administer at home, which is why it is important to note the dosing schedule. In addition, because it is an oral chemotherapy agent, temozolomide requires the same handling and administration precautions as all other chemotherapy. Unlike the many other oral chemotherapy agents, temozolomide requires co-administration with an anti-emetic to prevent nausea and vomiting. Lastly, it is important to note that temozolomide can be given with or without food, but that consistency must be maintained (i.e. always with food or always on an empty stomach). For these reasons, it is important that any patient taking temozolomide receive extensive counseling on proper storage (i.e. in a locked cabinet away from children), handling, and administration of the medication. Additionally, they should be instructed on where to call if any questions arise.

While convenient due to its oral formulation, because of the aforementioned factors, temozolomide may not be the optimal treatment option for all patients. When it comes to picking between the agents, the choice should be based on patient and provider preference, as they have been shown to have similar response when compared head to head.[17] While these two agents did show minimal success in the previously mentioned trials, in general chemotherapy has not been shown to be very effective for the treatment of metastatic melanoma. Consequently, much study and research is ongoing to find alternative effective treatment options for metastatic melanoma.

Targeted Agents

As researchers discover more about metastatic melanoma, the healthcare community has learned that not all patients with metastatic or unresectable melanoma have the same type of tumor. One of the most investigated genetic mutations in melanoma encodes for a protein kinase (enzyme acting on proteins to modify them) found in the MAPK pathway, which is a pathway that mediates a cell's response to growth signals. This particular protein is called BRAF, and is a member of the RAF kinase family, one of the enzyme groups in the MAPK growth pathway.[18] More specifically, the BRAF V600E mutation is responsible for 90% of melanoma BRAF mutations. Alteration of the BRAF kinase leads to the hyper-activation of the MAPK pathway and with this unregulated growth stimulation, tumor development is likely. The BRAF V600E mutation is found in up to 60% of melanomas. However, no prognostic significance in comparison to melanomas without this mutation has been demonstrated to date.[19] Once diagnosed with metastatic dis-

ease, patients will undergo genetic testing to screen for the BRAF gene mutations. For patients with disease positive for the BRAF V600E mutation, targeted therapy is a preferred treatment option.[6] Two of these options, vemurafenib (Zelboraf) and dabrafenib (Tafinlar) work by inhibiting the mutant BRAF kinase.[20,21] Treatment with these agents blocks replication and survival of the tumor cell. Both medications are FDA-approved specifically for the treatment of metastatic melanoma with BRAF V600E mutation.

While they have not been compared head to head, both vemurafenib and dabrafenib have shown significant improvement in overall survival and progression-free survival over chemotherapy with dacarbazine.[17,22] Vemurafenib was compared to dacarbazine in patients previously untreated for stage 3 or 4 melanoma. The median overall survival in patients receiving vemurafenib was 13.2 months, compared to 9.6 months in patients receiving dacarbazine.[22] Patients in the vemurafenib group began showing a response to therapy about 1.5 months into treatment, which was significantly faster than the 2.7 months that patients in the dacarbazine group took to respond. In a similar trial design, dabrafenib was compared to dacarbazine in previously untreated patients with stage 3 or 4 melanoma. Those receiving dabrafenib had a progression-free survival of 5.1 months, while the progression-free survival in those receiving dacarbazine was only 2.7 months.[23] In addition, similar to vemurafenib, patients receiving dabrafenib showed a response about 6 weeks into treatment. Though patients had a fairly quick response to treatment with dabrafenib, the duration of this response was about 5 months, while those receiving dacarbazine continued to maintain response at the time that the trial was published. In these studies, the adverse effects seen with vemurafenib and dabrafenib were similar.[20-23] Major side effects of vemurafenib and dabrafenib include: headache, fever, peripheral edema (water retention), rash, photosensitivity (sensitivity to light), hair loss, nausea, vomiting, diarrhea, muscle aches, and limb pain. The major toxicity difference between the two agents is that dabrafenib is associated with more thickening of the skin (hyperkeratosis) than vemurafenib, while vemurafenib is associated with a greater incidence of secondary skin neoplasms (cancers) than dabrafenib.[20,21] Unfortunately, because of their similar efficacy and toxicity profile, it may be possible that certain patients cannot tolerate either of these targeted therapy options.

Vemurafenib is dosed at 960 mg twice daily by mouth until evidence of disease progression or unacceptable toxicities.[20] Because it is available as 240 mg tablets, it is important to note that patients should be taking 4 tablets twice a day. Vemurafenib can be taken without regard to meals, but should ideally be taken about 12 hours apart. In addition to specifics regarding administration, it is also important to be aware that vemurafenib is associated with a number of drug-drug interactions. For patients taking multiple medications, performing an interaction check is of utmost importance. Dabrafenib is given as 150 mg twice daily by mouth until evidence of disease progression or unacceptable toxicity.[21] Unlike vemurafenib, dabrafenib is a capsule and is available as 50 mg and 75 mg. It is important to pay close attention to the capsule strength that a patient is receiving so as to avoid a labeling error when indicating the number of capsules a patient should be taking twice daily (i.e. 2 capsules twice daily versus 3 capsules twice daily) and the number of capsules being filled for a one month supply (i.e. 120 capsules versus 180 capsules). Another major difference from vemurafenib is that dabrafenib should be administered on an empty stomach, at least 1 hour before or 2 hours after a meal. Like vemurafenib, dabrafenib is also associated with a number of drug-drug interactions. In fact, both drugs interact with many of the same medications.[20,21] Some of these include medications that are metabolized through the cytochrome P450 enzyme system such as voriconazole, ketoconazole, clarithromycin, and ritonavir. In addition, because both vemurafenib and dabrafenib can cause cardiac problems, they should not be combined with other medications that do the same, such as amiodarone, escitalopram, and fluoxetine. Lastly, patients should know that even though both vemurafenib and dabrafenib are oral medications, they are still required to follow-up regularly with their providers to monitor lab values and to assess efficacy and toxicity.

Test Your Knowledge #1:

Dispensing Hazardous Medications
Sarah is a 35 year old woman who comes into the pharmacy to drop off a prescription for a new medication. The prescription is written as follows:

Zelboraf 960 mg PO BID #60

What points need to be addressed?

_____

_____

_____

_____

Trametinib, brand name Mekinist, is another targeted therapy that may be an option in patients unable to tolerate vemurafenib or dabrafenib. Trametinib also works by inhibiting mutated BRAF kinases; more specifically, it works on MEK1 and MEK2 enzymes, which are a type of BRAF kinase that are found at a different step along the MAPK pathway compared to the previously mentioned agents.[18] In addition to BRAF V600E mutation, trametinib is also approved to treat metastatic melanoma with BRAF V600K mutation.[24] It is administered at a flat dose of 2 mg by mouth once daily. The administration of trametinib with food has been shown to increase levels in the blood by 24%, so it must be taken at least 1 hour before or 2 hours after a meal. Trametinib is available as 0.5 mg and 2 mg tablets and must be stored in the refrigerator in its original bottle. One advantage that trametinib may provide over vemurafenib or dabrafenib is its lack of any major known drug-drug interactions. Trametinib has shown improvement in progression-free survival when compared to chemotherapy agents dacarbazine or paclitaxel.[25] In a phase 3 study of patients with advanced or metastatic melanoma, trametinib showed a progression-free survival of 4.8 months, while chemotherapy demonstrated a progression-free survival of 1.5 months. However, similar to dabrafenib, the response to trametinib lasted about 5.5 months. The side effect profile of trametinib is slightly different than the previously mentioned targeted agents.[24,25] Common side effects include: peripheral edema, rash, acne-like rash, diarrhea, abdominal pain, mouth sores, and fatigue.[24] Because vemurafenib, dabrafenib, and trametinib are all orally administered, they are equally convenient. In terms of efficacy, though they have not been directly compared, all three agents appear to produce a fairly quick, but short-lived, tumor response. Therefore, the choice between the three targeted therapies is often dependent on insurance coverage, side effect profiles, and patient and provider preference.

Approval of the new targeted agents has created a novel treatment approach in metastatic melanoma patients with tumors expressing specific BRAF mutations. These responses seem to have a quick onset; however, they have not shown durable disease control. As these are provided in a convenient oral dosage form with an improved side effect profile compared to previous standard treatments, development of further targeted agents is expected.

Immunotherapy

Another important aspect of melanoma is that it is an antigenic tumor.[26] This means that melanoma tumors secrete proteins that the immune system can detect as foreign and then mount an attack against. This knowledge was gained through further investigation into cases of melanoma tumors that were reported to have spontaneously regressed. In addition, biopsies of melanoma tumors have shown that melanoma tumors contain immune cells, suggesting that the immune system was attacking the melanoma tumor. Lastly, the risk of melanoma has been shown to be higher in patients who are immunocompromised (impaired immune system), which further supports the idea that the immune system is involved in fighting melanoma.[27-29] Therefore immunotherapy is another approach to the treatment of metastatic melanoma. Interleukin-2 (IL-2) or aldesleukin, brand name Proleukin, and ipilimumab, brand name Yervoy, are the only currently approved immunotherapy agents to treat metastatic melanoma.[6]

Similar to IFN- a 2b and pegylated interferon, IL-2 works by mimicking chemicals within the body. Once IL-2 is inside the body, it works like the body's internal IL-2, which leads to the release of chemicals creating an anti-tumor response.[30] In addition to treatment of metastatic melanoma, IL-2 is also FDA-approved for use in metastatic renal cell carcinoma. For the treatment of metastatic melanoma, IL-2 is given at a dose of 600,000 international units/kg/dose. Patients receive a dose intravenously over 15 minutes every 8 hours for a total of 12-15 doses. Each vial of IL-2 contains 22 million international units lyophilized powder. Each vial should be reconstituted with 1.2 mL sterile water for injection to a final concentration of 18 million international units (1.1 mg/mL). The final dose should be further diluted in 50 mL of D5W. As a general rule, the final concentration of the medication should be greater than 30 mcg/mL and less than 70 mcg/mL. Of note, before and after reconstitution, IL-2 should be stored in the refrigerator. However, the final dilution must be brought to room temperature prior to administration. It is important not to shake the medication at any point during the preparation or administration process. Unlike chemotherapy, clinical studies have shown that IL-2 can produce a complete and durable response in a select patient population.[31] Of the patients who achieved a complete response with IL-2 therapy (5%), 59% maintained their response at an average follow-up time of 62 months. Though effective, IL-2 is also fairly toxic and requires patients to be admitted to the hospital for close observation to receive therapy. In fact, patients are assessed by a healthcare

provider around the clock during therapy to ensure that it is safe for the patient to continue therapy and receive the next dose. Because of the strict monitoring of IL-2 therapy, the pharmacy should confirm that the patient is cleared to continue with treatment prior to the preparation of each dose. Side effects experienced by patients receiving IL-2 therapy include: fever, chills, confusion, low blood pressure, increased heart rate, shortness of breath, nausea, vomiting, diarrhea, acute (sudden onset) kidney failure, and low blood cell counts **(Table 2).**[30,31] In spite of the high toxicity risk, IL-2 is a promising treatment option for patients with metastatic melanoma, particularly patients who are in otherwise good health with minimal other medical problems.

Ipilimumab is another type of immunotherapy that was designed to support and enhance the patient's natural antitumor response. It was approved in 2011 by the FDA for the treatment of metastatic melanoma.[32] It works by inhibiting cytotoxic T-lymphocyte antigen 4 (CTLA-4), which leads to increased activity of the immune system against the melanoma tumor. In short, ipilimumab is designed to keep the patient's immune system constantly "turned on" or in "attack mode". It is dosed based on weight at 3 mg/kg and is given intravenously over 90 minutes every 3 weeks for a total of 4 doses. Ipilimumab is available as 50 mg and 200 mg vials of intravenous solution (concentration of 5 mg/mL), which should be stored in the refrigerator. When preparing ipilimumab, it is important to first allow the vials of drug to come to room temperature. The medication should be further diluted in either 0.9% NaCl or D5W to a final concentration of 1-2 mg/mL. Like IL-2, ipilimumab should not be shaken at any point during the preparation or administration process. Ipilimumab was studied with a theoretical melanoma vaccine, glycoprotein 100 (GP-100), in previously treated patients with stage 3 or 4 melanoma.[33] Patients received either ipilimumab plus GP-100, ipilimumab alone, or GP-100 alone. In this study, ipilimumab showed about a 12% overall response rate and demonstrated median overall survival of 10 months, supporting the efficacy of ipilimumab in the treatment of melanoma. One thing to note is that unlike targeted therapy, patients who receive therapy with ipilimumab and GP-100 maintained their response for an average of 11 months. Additionally, long-term follow-up from clinical trials report numerous durable responses maintained for several years.[34] As ipilimumab is stimulating the immune system to attack the melanoma tumor it can take time to achieve its goal. Therefore, a variety of new clinical response patterns have been documented, ranging from slow and steady reductions of tumors to responses documented 12-weeks into treatment after initial increases in tumor burden.[35] These findings suggest that the application of conventional tumor response criteria and the initiation of ipilimumab to patients with rapidly progressing disease unable to tolerate a potential delay in response may not be appropriate.

Because ipilimumab is an immunotherapy agent, many of its side effects are considered to be a result of its alteration of immune function and are classified as immune-related adverse events (irAEs) **(Table 2).**[32,33] Fever, confusion, headache, visual changes, neuropathy (numbness and tingling), weakness, skin rash, and itching are all considered irAEs. To ensure safe use of ipilimumab, monitoring for the signs and symptoms of the irAEs before each dose is essential. Dosing adjustments should be made based on the severity and duration of irAE resolution. One body system in particular

Table 2. Immunotherapy[26-31]

Medication	Mechanism of Action	Adverse Events
Ipilimumab	CTLA-4 Inhibitor	• Fever • Confusion, headache, visual changes • Abnormal liver tests, jaundice • Nausea, vomiting, diarrhea, abdominal pain • Neuropathy (sensory and motor), weakness • Skin rash, pruritis
High Dose IL-2	Elicits anti-tumor response through stimulation of cytokine release	• Fever, chills • Confusion • Hypotension, tachycardia • Progressive shortness of breath • Nausea, vomiting, diarrhea • Acute kidney failure • Anemia, thrombocytopenia

that is susceptible to irAEs is the gastrointestinal (GI) system. Nausea, vomiting, diarrhea, and abdominal pain are common GI irAEs. Management of irAEs focuses on the use of corticosteroids and can be guided by information found in the risk evaluation mitigation strategy (REMS) materials which provide explicit irAE diagnosis and treatment recommendations. Treatment discontinuation is recommended in the presence of persistent moderate adverse reactions, inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day or severe life-threatening adverse events. Although the side effect profile for ipilimumab is challenging, it does not require inpatient admission or administration as required with IL-2.

Test Your Knowledge #2:

Preparation of Hazardous Medications
In the daily batch of hazardous medications, there is an order for ipilimumab. The order is written as follows:

Ipilimumab 240mg IVPB over 90 minutes
every 3 weeks

How should the medication be prepared?

_____
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Clinical Application

When checking prescriptions, preparing, and dispensing prescription for any of the aforementioned medications, there are a few things to keep in mind. First, even though many of these treatment options are not categorized as chemotherapy (i.e. immunotherapy or targeted therapy), it is important to take appropriate precautions when preparing them. First, when preparing any intravenous or subcutaneous medications, it is important to do so in the appropriately certified space for the preparation of hazardous medications.[36] Any spills during preparation or administration should be promptly reported and cleaned up in accordance with institutional policies and procedures. Disposal of any unused or wasted medications should be done appropriately and in accordance with institutional hazardous medication policies and procedures. Regarding the oral dosage forms, it is important to have a separate counting tray for these agents, as they are hazardous medications. In addition, like all other medications, it is important that they are stored and dispensed according to the package labeling. For example, the package insert for trametinib states that the medication must be refrigerated and dispensed in its original container.[22] This is important to convey to all patients, especially those with pillboxes, as they would not be able to include trametinib in their pillboxes. Another key regarding these oral medications is making sure not to cut, crush, chew, or open any of them. Aerosolizing any of these medications could be harmful, as they are considered hazardous. Furthermore, it is important to read the package labeling regarding what to do when a dose of any of these medications is missed. Some medications may have a specific time window in which it is still acceptable to take the medication, while others will state that the dose should be skipped entirely. For example, the labeling of dabrafenib states that it is acceptable to administer a missed dose up to 6 hours prior to the next dose, while the trametinib labeling states that a missed dose should not be taken within 12 hours of the next dose.[20,22]

Lastly, it is important to remind patients that their oral medication is a hazardous medication and should not be disposed of in the garbage. Instead, they should be counseled to bring the medications back to the pharmacy, cancer clinic, or contact the manufacturer for appropriate disposal. As healthcare professionals, it is important to be aware of the details surrounding these medications to help ensure the safety of all of those involved in the medication preparation, administration, and disposal process.

Though there are a number of treatment options available for patients with metastatic melanoma, how is the treatment decision made between chemotherapy, targeted therapy, and immunotherapy? These three categories of therapy have not been directly *(continued page 16)*

Figure 1: Layers of the Skin

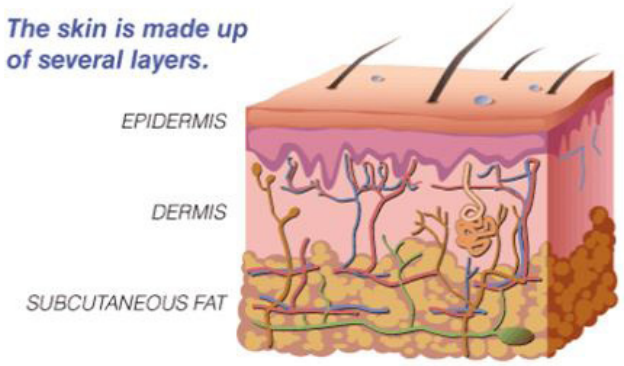

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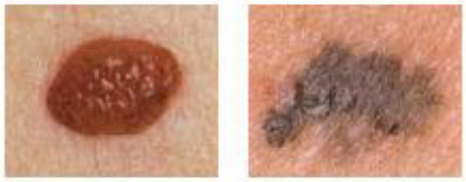
Figure 3. ABCDEs of Melanoma

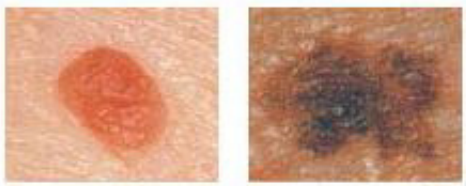
A=Asymmetrical

B=Borders



C=Color

D=Diameter



E=Evolution

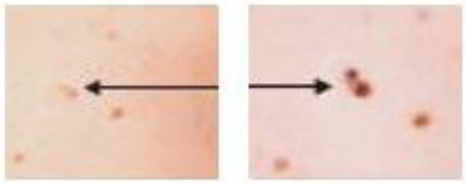


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Figure 5: Classification of Tumors

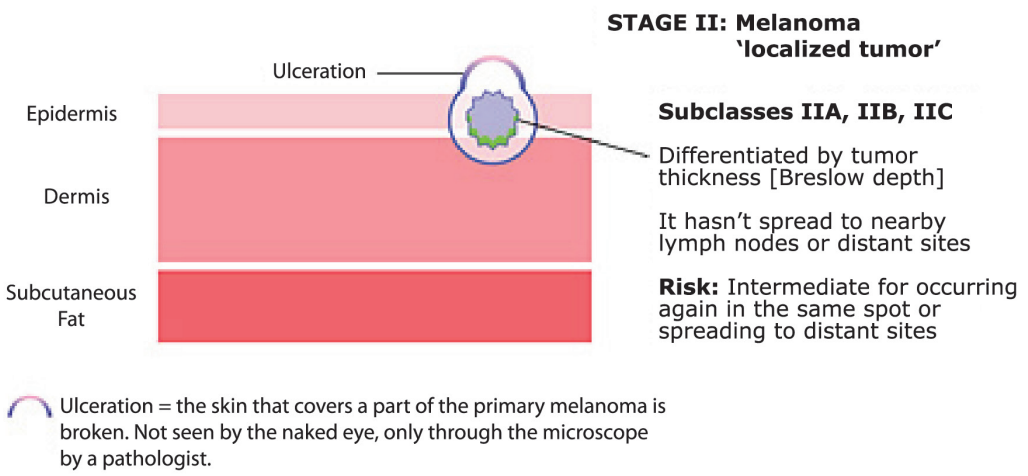
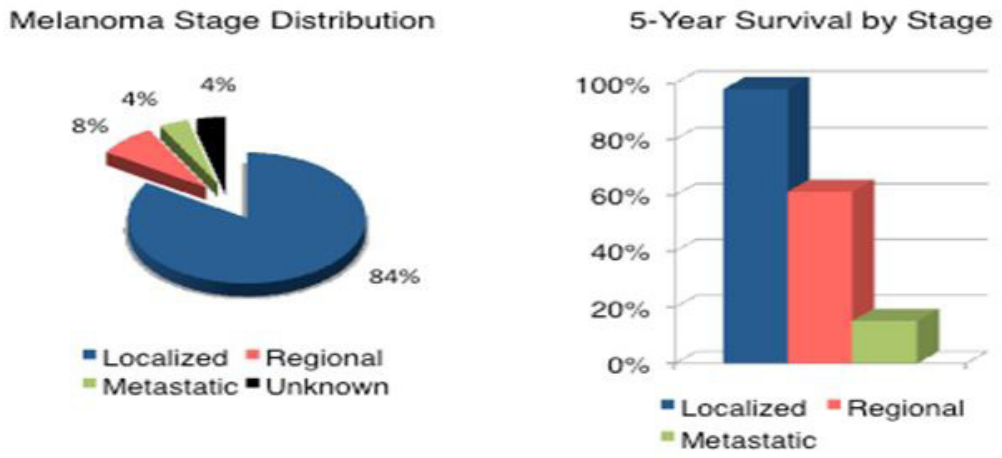


Figure 7. Statistics on Staging[3]



compared in patients with metastatic melanoma, but based on the response rates, survival data and NCCN recommendations, chemotherapy may be the least effective option of the three.[9] In patients with genetically mutated metastatic melanoma, targeted therapy appears to result in a response, though the response may not be durable. Because of the fairly short-lived response to currently available targeted therapy, investigators are continuing to explore the new targeted therapy pathways and combination therapy. Recently, in January 2014 the combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) received accelerated approval from the Food and Drug Administration (FDA).[37] This approval was based on an overall response rate of 76% with combination therapy versus 54% in patients receiving dabrafenib monotherapy (150 mg twice daily). In addition, the combination therapy showed a median duration of response of 10.5 months, compared to 5.6 months with monotherapy. Furthermore, a currently ongoing study is comparing treatment with the combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally to two placebos for 12 months.[38] Lastly, immunotherapy has been the only approach to result in durable responses in metastatic melanoma patients. The major limitation to the use of immunotherapy is its toxicity profile and potential for delayed response with ipilimumab. These agents may not be the best treatment options in patients with significant co-morbidities (other disease states) or with rapidly progressive disease. Research is currently underway in order to develop an immunotherapy agent with enhanced efficacy and tolerability.

Test Your Knowledge #3:

Match Each Medication to Its Therapeutic Category
(answers can be used more than once)

___ Vemurafenib

___ Dacarbazine

___ Ipilimumab

___ Interleukin-2

___ Trametinib

___ Temozolomide

___ Dabrafenib

A. Chemotherapy
B. Targeted therapy
C. Immunotherapy

Conclusion

Skin cancers are a very real concern with an increasing incidence each year. Knowing the risk factors and the appropriate prevention and screening strategies is essential to allow diagnosis of all types of skin cancers at their earliest stages, optimizing treatment options and patient survival. For patients diagnosed with later or advanced melanoma, treatment options have improved with the recent approval of targeted therapies and immunotherapy agents. As previously mentioned, the new targeted agents are administered in an oral formulation resulting in a much different dispensing process than with previous melanoma therapies. Pharmacy technicians can play an important role in this process by assisting the pharmacist with acquiring the medication, preparing the medication, insurance approval, and communicating with patients.

References

1. Miller AJ, Mihm MC Jr. Melanoma. *N Engl J Med* 2006 Jul 6; 355 (1):51-65.
2. NCCN guidelines for patients: Melanoma. Accessed at: http://www.nccn.org/patients/guidelines/melanoma/index.html#8 on Jan, 2014.
3. Melanoma surveillance epidemiology and end results. Accessed at: http://seer.cancer.gov/statfacts/html/melan.html on 22 Oct, 2013.
4. Fortes C, Mastroeni S, Bakos L, et al. Identifying individuals at high risk of melanoma: a simple tool. *Eur J Cancer Prev* 2010 Sep;19 (5):393-400.
5. Skin Cancer Foundation: Suncreen. Accessed at: http://www.skincancer.org/prevention/sun-protection/sunscreen on Jan, 2014.
6. Guibert P, Mollat F, Ligen M, et al. Melanoma screening; report of a survey in occupational medicine. *Arch Dermatol* 2000;136:199-202.
7. American Cancer Society: Skin Exams. Accessed at: http://www.cancer.org/cancer/skincancer-melanoma/moreinformation/skincancerpreventionandearlydetection/skin-cancer-prevention-and-early-detection-skin-exams on Jan, 2014
8. Melanoma Research Foundation. Mucosal Melanoma. Accessed at: http://www.melanoma.org/understand-melanoma/what-is-melanoma/mucosal-melanoma on May, 2014
9. Coit DG, Thompson JA, Andtbacka R, et al. NCCN Clinical practice guidelines in oncology (NCCN Guidelines): Melanoma. Version 2.2014.
10. Merck & Co, Inc. Intron A (package insert). New Jersey: Merck & Co, Inc., 2011.
11. Merck & Co, Inc. Sylatron (package insert). New Jersey: Merck & Co, Inc., 2012.
12. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of Eastern Cooperative Oncology Group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res* 2004;10(5):1670-1677.
13. Eggermont AM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet* 2008;372(9633):117-26.
14. Teva Parenteral Medicines, Inc. DTIC (package insert). California: Teva Parenteral Medicines, Inc., 2007.
15. Merck & Co, Inc.. Temodar (package insert). New Jersey: Merck & Co, Inc., 2013.
16. Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006;24:4738-45. Epub 2006 Sep 11.
17. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000;18:158-66.
18. Davies H, Bignell GR, Cox C et al. Mutations of the BRAF gene in human cancer. *Nature* 2002;417(6892):949-954. Epub 2002 Jun 9. DOI 10.1038/nature00766
19. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 201;10:1239-1246. Epub 2011 Feb 22. DOI 10.1200/JCO.2010.32.4327.
20. Genentech, Inc. Zelboraf (package insert). California: Genentech, Inc., 2013.
21. GlaxoSmithKline, Inc. Tafinlar (package insert). North Carolina: GlaxoSmithKline, Inc., 2013.
22. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507-16. Epub 2011 Jun 5.
23. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012;380:358-65. Epub 2012 Jun 25.
24. GlaxoSmithKline, Inc. Mekinist (package insert). North Carolina: GlaxoSmithKline, Inc., 2013.
25. Flaherty K, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *New Engl J Med* 2012; 367: 107 – 14.
26. Guerry D. The cellular immunobiology of melanoma. In: Miller SJ, Maloney ME, eds. *Cutaneous Oncology: Pathophysiology, Diagnosis and Management*. Malde, MA: Blackwell Science.1998:211-217.
27. Sznol M. Betting on immunotherapy for melanoma. *Curr Oncol Rep* 2009;11:397-404.
28. Komenaka I, Hoerig H, Kaufman HL. Immunotherapy for melanoma. *Clin Dermatol* 2004;22:251-265.

29. Frankenthaler A, Sullivan RJ, Wang W, et al. Impact of concomitant immunosuppression on the presentation and prognosis of patients with melanoma. *Melanoma Res* 2010;20:496-500.
30. Novartis Vaccines and Diagnotics, Inc. Proleukin (package insert). California: Novartis Vaccines and Diagnotics, Inc., 2008.
31. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999;17:2105-16.
32. Bristol-Myers Squibb Company. Yervoy (package insert). New Jersey: Bristol-Myers Squibb Company, 2013.
33. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010 Aug;363:711-23. Epub 2010 Jun 5.
34. Farolfi A, Ridolfi L, Guidoboni M et al. Ipilimumab in advanced melanoma: reports of long-lasting responses. Melanoma Res 2012;22:263-270.
35. Pennock GK, Waterfield W, Wolchok JD. Patient Responses to ipilimumab, a novel immunopotentiator for metastatic melanoma: how different are these from conventional treatment responses? *Am J Clin Oncol* 2011 Feb17. [Epub ahead of print] DOI 10.1097/COC.0b013e318209cda9.
36. CDC Workplace Safety and Health. Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Accessed at: https://www.osha.gov/SLTC/hazardousdrugs on Feb, 2014.
37. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations. *N Engl J Med* 2012; 367:1694-1703.
38. NCT01682083. Accessed at: http://clinicaltrials.gov/show/NCT01682083 on Feb, 2014.

ANSWER KEY: TEST YOUR KNOWLEDGE EXERCISES

Exercise #1:

- Zelboraf is available as 240 mg tablets – each dose is 4 tablets total
- Monthly supply = 240 tablets

Exercise #2:

- Appropriate personal protective equipment should be donned and medication should be prepared in accordance with institutional hazardous medication preparation policy
- Obtain the drug from the refrigerator and allow vials to come to room temperature; do not shake vials
- Draw up 48 mL of drug
  ¤ 240 mg ÷ 5 mg/mL = 48 mL
- Dilute drug into 120-240mL 0.9% NaCl or D5W to a final concentration 1-2 mg/mL
  ¤ 240 mg ÷ 120mL = 2mg/mL
  ¤ 240 mg ÷ 240mL = 1mg/mL
- Deliver drug to the patient's nurse taking care not to shake the medication

Exercise #3:

_B_ Vemurafenib
_A_ Dacarbazine
_C_ Ipilimumab
_C_ Interleukin-2

_B_ Trametinib
_A_ Temozolomide
_B_ Dabrafenib

ANSWER KEY: CASE STUDIES

Part 1:

Family history
Fair complexion (hair, eyes, freckles)
Numerous moles
Excessive exposure to UV light and frequent sun burns

Part 2:

A Asymmetrical
B Border irregularities
C Color
D Diameter
E Evolution