Abbreviations

MELANOMA

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Learning Objectives

1. Devise an appropriate screening plan that accounts for patient-specific risk factors that should be elucidated in all individuals to prevent disease or aid in earlier detection of suspicious melanocytic lesions.
2. Given an individual patient's information, classify his melanoma using the various classification schemes—Clark's levels, Breslow's classification, and tumor-node-metastasis (TNM)—that compose the American Joint Committee on Cancer's staging of melanoma.
3. Evaluate the role of the diagnostic and treatment procedures involved in staging melanoma (i.e., surgical excision and sentinel lymph node dissection).
4. Devise an appropriate treatment regimen for a given patient at any stage and prognosis of melanoma, taking into consideration patient-specific factors.
5. Based on patient-specific factors and a given treatment regimen, develop a supportive care plan for toxicity prevention, monitoring, and patient education for each individual drug or biological in the regimen.
6. Apply physiologic principles of the immune system to assess the role of biochemotherapy, as well as the potential use of vaccines, for the treatment of melanoma.

Introduction

The most common site of cancer development in humans is the skin. Even in the face of increased public awareness of the deleterious effects of sun exposure, the incidence of cutaneous melanoma has continued to increase dramatically over the past 3 decades. Although the disease is curable in its early, localized form, the overall survival rate has not improved substantially for advanced disease, and management of invasive melanoma remains a daunting therapeutic challenge.

Epidemiology

The American Cancer Society estimates that 62,190 Americans will be diagnosed with melanoma, and 7910 will die from the disease in 2005. Although the incidence of melanoma climbed from 7.9 to 17.7 per 100,000 persons in the United States between the years of 1975 and 2000, these projections may be underestimations of the true incidence, especially because many cases of superficial and *in situ* melanoma are treated in outpatient clinics and often go unreported.

In the year 2000, 1 in 82 women and 1 in 58 men in the United States had a lifetime risk of developing some form of melanoma. Despite the fact that men are slightly more at risk for skin cancer development, melanoma is the leading cause of cancer in women ages 20–29. Overall, melanoma is the fifth most common malignancy in men and sixth most common in women, accountable for 5% and 4% of all new cancer cases, respectively. There is an increase in melanoma incidence with every decade of life, with the average age of diagnosis occurring at age 53. Even though melanoma affects a broad age range, 75% of all patients are under 70 years old, and the disproportionate mortality in younger and middle-age individuals results in a very high mean of 18.6 years of potential life lost for each melanoma death in the United States.

Light-skinned patients with a fair complexion are most at risk for melanoma; Caucasian populations are more commonly affected than non-Caucasians. Geography also plays a pivotal role in epidemiologic distribution of melanoma. This is particularly evidenced by the fair-skinned peoples of the subequatorial provinces of Australia and New Zealand, which are ranked first in the world in regard to melanoma incidence (greater than 30 cases per 100,000 individuals). In general, African Americans, Hispanics, and Asians are one order of magnitude less likely to develop melanoma compared with Caucasians. Highly pigmented

Abbreviations in this Chapter

5-HT_3	5-hydroxytryptanine type 3 receptor
AJCC	American Joint Committee on Cancer
Bcl	B-cell lymphoma derived protein
CDKN	Cyclin-dependent kinase inhibitor
CVD	Cisplatin, vinblastine, and dacarbazine
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GADD	Growth arrest and DNA damage-inducible enzymes
HDNS	Hereditary dysplastic nevus syndrome
HIV	Human immunodeficiency virus
IL	Interleukin
LDH	Lactic dehydrogenase
TNM	Tumor-node-metastasis
UV	Ultraviolet

individuals are more likely to have lesions occur on non-pigmented areas of their body, such as the palms and soles of hands and feet, which are areas typically less exposed to sun. For example, African Americans present more commonly with lesions found on the foot, which are usually of the acral lentiginous type.

Although the non-melanoma basal and squamous cell carcinomas account for more than 95% of skin cancers, it is cutaneous melanoma that accounts for the greatest number (79%) of skin cancer deaths. Noncutaneous melanomas do exist; these often occur in the pigmented cells of the retina and on mucous membranes of the nasopharyngeal sinuses, vulva, and anal canal. These noncutaneous tumors often present as malignancies that are more advanced and aggressive, and are rarely curable. However, more than 90% of melanomas are cutaneous lesions, and the relative survival rates, based on data from the Surveillance, Epidemiology and End Results program, have been increasing since 1975–79. Compared with that period, the melanoma 5-year overall survival rate has increased from 82.0% to 89.8% for all disease stages, as reported for the year 2000.

Although efforts to discover and refine new therapeutic approaches continue, particularly for advanced-stage disease, a more recent research thrust has been in the area of early diagnosis. It is hoped that by improving the methods for screening and identifying high-risk individuals before disease onset, and by increasing public awareness of the need for sun avoidance and protection, the incidence of melanoma can be drastically reduced.

Pathophysiology of Melanoma

Definitions

Malignant melanoma is thought to arise from melanocytes, which are pigmented dendritic cells, usually located in the epidermis, that produce melanin. Melanocytes are dispersed throughout the body in a variety of tissues other than the integumentary system, including the respiratory tract, alimentary tract, meninges, and lymph node capsules. Even though primary melanoma can occur in many anatomical locations, more than 90% are cutaneous melanomas. Melanin is synthesized from tryptophan-converted tyrosine in melanocytes, and this pigment is used to protect the body from the deleterious effects of ultraviolet (UV) radiation. A cluster of melanocytes makes up nevi, typically referred to as moles, and melanoma results when the melanocytes undergo a malignant transformation either in nevi or non-nevi melanocytes. Although conversion of melanocytes to cancer is likely due to the combination of sun exposure, genetics, faulty DNA repair pathways and other risk factors, the mutagenic effects of UV solar radiation on DNA are well established.

Pathogenic Effects of Ultraviolet Light

The constellation of effects that UV radiation causes in the skin includes the generation of cellular DNA crosslinks, a reduction in cutaneous immune response, increases in production of tissue growth factors, and the formation of melanin-derived reactive oxygen species, all of which aid in the development and maintenance of a malignant transformed cell. Ultraviolet radiation is contained within the spectrum of electromagnetic radiation that includes x-rays, gamma rays, visible light, and longer wavelength radiation, such as microwave radiation. In the wavelength range of UV radiation, photons are highly energetic and can initiate photochemical reactions in biological molecules. The etiology for melanoma development is commonly attributed to UV light and radiation, predominantly from sunlight. Ultraviolet radiation is divided into three regions: UVC 200–290 nm; UVB 290–320 nm; and UVA 320–400 nm. Ultraviolet C light, though highly toxic, is completely absorbed by the atmosphere of the Earth and is not a relevant factor for sun-induced tumorigenesis.

Environmental exposure to UVB light is thought to be the most dangerous, as only part of its rays are absorbed by the atmospheric ozone layer. The collagen-rich dermis presents a light-scattering barrier to the effects of UV radiation, whereas the stratum corneum and epidermis absorb much of the UVB radiation. Melanin, present in the stratum corneum, absorbs large amounts of UVB radiation, transforming this energy into heat that is dissipated between hairs or capillary vessels before it reaches DNA molecules in the skin cells. The direct effects of such UV radiation on skin cells can include DNA-strand breakage, base-pair damage, and faulty pyrimidine dimerization, leading to malignant transformation in susceptible cells. The incorrect repair of direct base damage or other base pair mismatches can also lead to mutations. Ultraviolet A light is not absorbed at all by the atmosphere, and though commonly not considered dangerous because it falls in a less energetic waveband, exposure to UVA radiation is being increasingly investigated for its carcinogenic and photoaging potential. Although UVA radiation does not appear to cause UV-induced base pair damage directly, an indirect mechanism in which DNA-damaging reactive oxygen radicals are formed has been described. Resultant effects of

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UV-induced DNA damage and the lack of repair of this damage are thought to be responsible for the development of cutaneous carcinogenesis. The resulting disturbances in oncogenic, tumor-suppressive, and cell-cycle control signaling pathways that are perpetuated by such radiation is thought to be pathogenic. Melanoma typically results from UV-induced mutations that activate the *ras* pathway, as well as inactivate the p16 and p53 tumor suppressor genes.

The p53 gene is a stress-response gene that encodes an oncosuppressive nuclear protein. After exposure to UV radiation, the p53 gene is initially upregulated, causing overexpression of p53 protein, which ultimately leads to a subsequent inactivation of the p53 gene through a negative autoregulatory feedback loop. This sequence of steps is observed in the apoptotic pattern of keratinocytes damaged by UVB radiation, but in that case results in the activation of programmed cell death or apoptosis. This "smart response" of the keratinocyte to self-destruct in response to DNA damage has never been reported in melanocytes. The presence of higher levels of anti-apoptotic proteins such as B-cell lymphoma-derived protein-2 (bcl-2) in melanocytes in comparison to keratinocytes may help explain the differences in response to DNA damage and the ability for malignant melanocytes to continue to proliferate. The p53 gene is widely expressed in the radial growth phase, vertical growth phase, and metastatic stages of melanomas, but the high degree of variability of this expression makes it ineffective for diagnosis. The p53 gene is also responsible for the regulation of other genes involved in melanoma development. Growth arrest and DNA damage-inducible genes (GADD45, GADD34, and GADD153) that are p53-regulated are often disregulated in melanoma.

Another tumor suppressor gene, p16, encodes for the p16 protein and is frequently inactivated in human tumors, including melanoma. The expression of p16 protein in the granular cell layer results in the protection of the epidermal cells from undergoing apoptosis in response to UV radiation. The overexpression and subsequent depletion of p16 protein in reaction to UV radiation can lead to the loss of the apoptotic mechanism in damaged cells, thereby blocking the initiation of programmed cell death. But in contrast to p53, the expression of p16 protein shows gradual down-regulation with the progression of the tumor, and complete loss of expression in metastatic tumors has been reported. The p16 protein is an upstream signal transducer of another tumor suppressor family of genes, Cyclin D kinase inhibitor (CDKN). The CDKN blocks the activity of Cyclin D1, which in part, regulates the kinase activities of other Cyclin D kinases, such as CDK2A, CDK2B, and CDK4; numerous studies have demonstrated that disregulation of CDK activity occurs in more than 95% of studied melanoma cell lines. In addition to the effect of UV radiation on point mutations and irregular DNA processing of this family of genes, the CDKN2A and CDKN4A genes have been implicated in the carcinogenesis of familial melanoma.

Exposures of melanocytes to UV radiation not only results in inactivation of tumor-suppressor genes, but can also lead to the activation of proto-oncogenes as well. The activation of these proto-oncogenes results in the excessive production of their gene products or structurally aberrant products resulting from point mutations or chromosomal translocations. The bcl-2 and *ras* genes are representative oncogenes that are correlated with melanoma growth. The bcl-2 protein is an integral membrane protein located in the membranes of the endoplasmic reticulum and nuclear envelope, and in the membranes of the mitochondria. Upregulation of the expression of the anti-apoptotic protein, bcl-2, confers to the cell the ability to resist apoptotic cell death signaling and the cytotoxic effects of chemotherapy, immunotherapy, and radiation.

As previously discussed, apoptosis triggered in keratinocytes that lack bcl-2 commits them to the process of keratinization followed by shedding. Melanocytes that are exposed to UV radiation and become malignant do not become apoptotic due in part to the suppressing effect of bcl-2 protein expression. This suppression provides a growth advantage to bcl-2 overexpressing epidermal cells, allowing the accumulation of oncogenic mutations over a prolonged time period. The bcl-2 has become an interesting target in melanoma therapy, leading to the development of antisense-directed therapeutic drugs.

The *ras* family of proto-oncogenes encodes small guanosine triphosphate-binding proteins involved in signal transduction of mitogenic signals sent from activated growth-factor receptors. This *ras* gene activation occurs following aberrant repair of UV-induced pyrimidine dimers. The eventual overexpression of the *ras* protein activates a signaling cascade that includes the Raf family of serine-threonine kinases, which activate MEK kinases that, in succession, help to phosphorylate and activate the MAP kinases ERK-1 and ERK-2. This maintained expression of *ras*-ERK is produced by the stimulation of epidermal growth factor receptor. Activating mutations of *ras* genes are relatively common in melanoma. The role of UV-induced *ras* mutagenesis and subsequent aberrant kinase activity indicates that there may be several targets along the signaling cascade for target drug inhibition. Multiple *ras* effector pathways also appear to play an important role in the regulation of Cyclin D1, offering another reasonable conduit for mutagenesis. Various novel kinase inhibitors that inhibit one or more targets along the *ras*-Raf-ERK oncogenic pathway are now being studied investigationally in the clinic.

Sunscreens and Prevention

Epidemiological studies over the past 2 decades have confirmed the direct relationship between excessive sun or UV exposure and skin cancer, yet only in the past few years have clinical studies confirmed that the use of sunscreens may reduce the likelihood of skin cancer. Although much of this chapter focuses on the treatment of melanoma, prevention is far more important.

For pharmacists, the education and counseling provided to patients about the proper use of sunscreens cannot be underemphasized as these products play a major role in skin cancer prevention. Pharmacists not only should have a complete knowledge of the current recommendations on the

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selection, use, and limitations of sunscreen usage, but should also provide guidance on the development of a total skin protection plan as they are the most accessible source of medical information for skin cancer protection. To provide optimal pharmaceutical care, pharmacists must also comprehend the impact of the patient's clinical characteristics, such as skin type, and the impact of lifestyles on a patient's overall risk of skin cancer development.

First, patients must be informed that all UV radiation exposure (natural or man-made) is harmful. Minimization of exposure includes wearing the appropriate clothing (long sleeves, hats, and UV-blocking sunglasses), avoiding the sun from 10 AM to 4 PM, and seeking shade, when available, outdoors. Use of broad-spectrum (UVA and UVB protection) sunscreens should be viewed as an adjunct for, not a replacement of, a sun protection plan. Patients should be informed that even slowly acquired "base tanning" damages DNA and does not protect from further skin damage, including melanoma. Because currently available data indicate that severe sunburns occurring during childhood and adolescence may greatly increase the likelihood of melanoma later in life, parents should be guided to closely regulate their children's UV radiation exposure.

Pharmacists should advocate that all individuals use broad spectrum sunscreens with sun protection factor values of 15 or greater, containing active ingredients that block both UVA and UVB radiation. Available UVA-blocking active ingredients, which block ultraviolet light in the range of 320–400 nm, include oxybenzone, sulisobenzone, dioxybenzone, methyl anthranilate, and avobenzone. Currently approved ingredients that block UVB radiation in the range of 290–320 nm include p-aminobenzoic acid, octyl methoxycinnamate, octyl salicylate, octyl dimethyl aminobenzoate, homosalate, and octocrylene. Zinc oxide and titanium dioxide absorb and scatter both wavelength ranges, making them ideal protective screens covering all wavelengths of UV radiation. Both compounds are now available in a micronized form making them less conspicuous on the skin and therefore more acceptable to consumers.

Although many of these sunscreen products are advertised as water resistant and possess sun protection factor ratings greater than 30, they should all be reapplied every 2 hours, or more frequently if swimming or if active sweating is involved, to provide maximum protection. To encourage the correct use of these products, the Food and Drug Administration (FDA) has new regulations prohibiting the use of expressions such as "waterproof" and "all day protection" in the labeling and advertising of these products. For individuals living in most locations in the United States, sunscreens should be used year around. Patients should be encouraged to use these products even on overcast days because more than 80% of harmful radiation can pass through fog and clouds. Because most individuals receive their greatest concentrated exposure to sunlight during leisure activities, people visiting beaches and ski areas should be made aware that snow, ice, sand, and altitude all greatly increase the UV dose reaching the skin.

It is especially important to apply sunscreens on body areas such as face, ears, neck, arms, shoulders, hands, feet, and back. Because most people apply less than 50% of the amount of sunscreen they should, it is important to reinforce that at least 1 ounce of sunscreen material should be used to cover the above noted areas.

Following the simple prevention guidelines not only greatly reduces the risk of skin cancers, but also has been shown to decrease the impact of photoaging on the skin.

Immunologic Influence

The development of melanoma, unlike the development of other solid tumor types, is characteristically under the influence of many immunologic factors. Where normal melanocytes require growth factor stimulation for proliferation, malignant melanocytes are able to proliferate without them. For melanoma, the concert of autocrine and paracrine influences yields a self-sustaining malignant cell possessing growth factors, proteases, cell adhesion proteins, and survival molecules sufficient to support independent growth and metastasis. Observation of expression of both developmental and tumor-specific antigens on tumor tissue, response of patients with advanced disease to cytokine therapy, and lymphocytic infiltration in certain tumors has dramatically added to our understanding of the complexities involved with tumor immunology.

Over the past decade, many of the most interesting findings concerning the genesis and treatment of melanoma have focused on the relationships between the host immune system and the disease itself. Indeed, most of the recent discoveries in the therapeutics of melanoma have been in the field of immunopharmacology, investigating the role cytokines, cell surface antigens and receptors, and antigenic systems play in melanoma genesis, growth, progression, recognition, and interaction with the host's immune system. The discovery of anti-melanoma antibodies, produced early in the natural history of the disease, suggests the role that the host immune system may play in the treatment of this disease. Melanoma, in contrast to many other solid tumors, is relatively resistant to "standard" treatment modalities, such as radiation and chemotherapy. Conversely, the development and proliferation of melanoma appears to be largely regulated by host immune function. Because of this, the potential for the development of immunotherapies for melanoma treatment is promising.

Spontaneous regression of melanoma, though uncommon, has been reported. Often the host's own immune system is the best indicator of tumor initiation and establishment. For instance, the presence of anti-melanoma antibodies against cell surface-bound melanoma-associated antigens in the serum of patients is evidence of a cellular and humoral response to such tumoral antigens. Vaccines developed to create antibodies targeting such antigenic proteins are being widely studied for treating melanoma. In addition, small molecule and oligonucleotide-based inhibitors of downstream malignant signaling processes to halt further cell growth and proliferation are at the forefront of new drug development for melanoma.

Bacillus Calmette-Guérin, a nonspecific immunologic stimulant, is known to elicit immune responses to tumor-associated antigens when given to patients with various

cancers. Bacillus Calmette-Guérin was the first immunostimulant studied in melanoma and it has helped to clarify the role of the immune response to the development of melanoma in humans. Although clinical trials have confirmed that Bacillus Calmette-Guérin is not a useful therapeutic drug, even in the adjuvant setting, there has been considerable proof of principal research performed with Bacillus Calmette-Guérin elucidating the role of the immune system in the genesis and perpetuation of melanoma. Proof of concept data drawn from Bacillus Calmette-Guérin research helped establish the framework from which tumor vaccine research has flourished.

Patient Risk Factors

Sun Exposure

Although the increase in melanoma incidence over the past 3 decades is not entirely understood, several lifestyle and environmental factors may be important. Environmental changes such as degradation of the Earth's ozone layer, coupled with lifestyle changes such as increased personal sun exposure due in part to the rise in outdoor recreational activities and indoor occupational environments, particularly for fair-skinned individuals in industrialized countries, may all be additive causal factors.

For instance, multiple epidemiologic studies suggest a direct correlation between the number of blistering sunburns an individual has received in his or her lifetime and the risk for cutaneous melanoma. In contrast, noncutaneous melanomas are linked to total sun exposure rather than to the severity of intermittent unprotected exposure. Individuals who have sustained such severe sunburns or prolonged episodic sun exposure in early life are considered to be at major risk for skin cancer in general.

Table 1-1. Risk Factors for Developing Cutaneous Melanoma

Risk Status	Relative Risk
Greatly Increased Risk	
Personal history of atypical moles, family history of melanoma, and greater than 75–100 moles	35
Previous nonmelanoma skin cancer	17
Congenital nevus (giant, > 20 cm)	5–15
History of melanoma	9–10
Family history of melanoma in parent, sibling, or child	8
Immunosuppression	6-8
Moderately Increased Risk	
Clinically atypical nevi (2–9)	4.9–7.3
No family history of melanoma/sporadic atypical nevi	
Large number of nevi	
(51–100)	3.0–5.0
(26–50)	1.8–4.4
Chronic tanning with UVA	5.4
Modestly Increased Risk	
Repeated blistering sunburns	
(3)	3.8
(2)	1.7
Freckling	3.0
Fair skin, inability to tan	2.6
Red or blond hair	2.2
Clinically atypical nevus (1)	2.3

LDH = lactic dehydrogenase.

Phenotypic Traits

Fairer complexions and an inability to tan are not the only risk factors associated with an increased susceptibility to cutaneous melanoma (Table 1-1). Other phenotypic traits associated with melanoma include lighter hair, especially blonde or red, and eye shades such as blue or green. Although eye color has not been found to significantly increase the risk of melanoma, blond- and red-haired individuals have been shown to have a 7-fold and 3.7-fold greater incidence of melanoma, respectively. Individuals with a total body count of greater than 50 pigmented lesions (nevi), an assortment of freckles or moles, are also at an increased risk. Although melanocytic nevi are often precursors to melanomas, the size and abundance of these more benign moles are more regularly used as markers to identify high-risk patients during screening. For example, patients with atypical nevi that are larger (greater than 6 mm in diameter), irregularly shaped, or various shades of color incur a 6% lifetime risk of melanoma development.

Inherited Traits

A family history of melanoma is also a risk factor, and about 10% of all people with melanoma have a family member who has had the disease. Depending on the number of affected relatives, the risk can be up to 8 times greater than that of an individual without a positive family history of melanoma. Familial atypical mole and melanoma syndrome is an autosomal dominant hereditary occurrence of melanoma that is reported in patients with a positive family history of melanoma and a preponderance of atypical moles. This syndrome is also known as hereditary dysplastic nevus syndrome (HDNS), and the lifetime probability of melanoma occurrence is nearly 100%.

Genetic predisposition to inherited mutations of the CDKN2A and CDKN4A genes is thought to be directly related to the occurrence of familial melanoma and can result in a 60%–90% lifetime risk of developing cutaneous melanoma. In addition, inherited mutations in the melanocortin-1 receptor (in normal melanocytes, a ligand-binding melanocortin that initiates the production of a sun-protective melanin) have been identified in red-haired individuals and those who are particularly photosensitive. This mutation may increase the lifetime risk of melanoma development by 3-fold. Diseases such as xeroderma pigmentosum, the result of an autosomal recessive trait reducing the ability to repair UV-induced DNA damage, have been shown to greatly increase the risk of skin cancer at an early age. At this point, routine genetic testing is not a standard practice and is currently only used as a research tool.

Abbreviations

Special Populations

Patients who are immunocompromised are also at a higher risk of developing melanomas. The behavior of melanoma in this population is typically much more aggressive compared with patients with normal immunologic function; therefore, skin cancer surveillance should also be more aggressive. The rapidly invasive nature of both cutaneous melanoma and non-melanoma skin cancer in such patients is often characterized by local invasion with or without regional metastases at the time of diagnosis, poor histologic differentiation, and local, regional, or systemic relapse after therapy.

Increased skin surveillance should be undertaken in patients with chronic lymphocytic leukemia, Hodgkin's disease, or a history of other hematologic malignancies. This group would also include patients who are currently on any immunosuppressive treatment regimen, including recipients of a solid organ or hematopoietic stem cell transplant. Annual screening, including detailed skin mapping, of these high-risk patients is imperative to reduce the incidence of melanoma in these populations. Patients who have had a prior cutaneous melanoma have a 10-fold greater risk than the general public for developing another primary lesion and therefore should follow the most rigorous skin surveillance procedures.

Pharmacists who educate the public about the benefits of early detection of lesions can emphasize the curative treatment options and help decrease overall melanoma mortality. Individual recommendations for a sun protection plan should be made by the pharmacist for patients who are receiving immunosuppressing drugs for a solid organ transplant and for individuals who are positive for the human immunodeficiency virus (HIV). These recommendations may vary and should be based on the overall impact of the complete therapeutic regimen these patients are receiving.

Patients With Solid Organ Transplant

Epidemiologic data indicate a 3.8–5-fold increased incidence of melanoma in patients with solid organ transplants. Variability in immunosuppressive regimens may be responsible for the differing incidence of melanoma among organ transplant types. Among solid organ transplants, the relatively older age at transplantation and higher dosage of immunosuppressive drugs used in patients with heart transplants can explain the significant increase in skin cancer-related morbidity and mortality compared with other solid organ transplant types. The incidence of melanoma in patients with kidney transplants is still high, especially in countries with high sun exposure rates, such as Australia and New Zealand. The incidence of melanoma in patients with liver transplants, in contrast, is lower than in patients with kidney transplants, which may be associated with the lower levels of maintenance immunosuppression used in this population.

Patients With Human Immunodeficiency Virus

Individuals infected with HIV who have malignant melanoma have significantly decreased disease-free and overall survival. Although no direct association has been made between the depth of the primary melanoma lesion at the time of presentation and $CD4^+$ cell count or disease stage, patients who are HIV-positive with melanoma and lower $CD4^+$ counts usually have a poorer prognosis. Although there are no current recommendations for screening patients who are infected with HIV for melanoma, a yearly full skin examination for all high-risk patients, including those with a positive family history, history of sunburns, or more than 50 typical or more than five atypical nevi, is recommended. Patients who have tested positive for HIV diagnosed with melanoma should also be extensively surveyed for metastatic disease. Patients with confirmed HIV should be followed every 3 months for 2 years and at least twice yearly thereafter.

Clinical Characteristics

Presentation

The diagnosis of melanoma involves attention to the shape, edges, color, and size of the melanocytic lesion, which is often described using the "ABCD" mnemonic for asymmetry, border irregularity, color variegation, and diameter, respectively. Unlike benign moles, the malignant nevi have a shape that is often asymmetric with marginally irregular borders. Although lesional colors vary, and are often nonhomogeneous, they are commonly tan, brown, or even black and can include hues that include red, purple, and white. A diameter of less than 6 mm is often used to distinguish benign moles from those that are suspicious for melanoma. Some professionals also add the letter "E" to the mnemonic, indicating the evolution of preexisting nevi is a characteristic of a suspicious lesion.

Other signs and symptoms associated with malignant nevi include itching, bleeding, ulceration, or pain at the site. The importance of careful, periodic self-examination, or whole body skin inspection by a physician for changes in preexisting atypical moles or lesions cannot be overemphasized. Sometimes serial photography of individual lesions and whole areas of skin, to compare over time, can aid in a clinic diagnosis.

The differential diagnosis of pigmented lesions can complicate the diagnosis of melanoma. The non-melanocytic lesions that resemble melanoma include seborrheic keratosis, subungual hematoma, compound nevus, junctional nevus, and lentigo (age spots). Some less common lesions that are also non-melanocytic include pigmented basal cell carcinoma, blue nevi, and vascular lesions such as those that appear resultant of Kaposi's sarcoma. The discrimination of cutaneous melanoma from certain atypical moles can be difficult; therefore, the excision and histologic examination of narrowly margined lesions (1–3 mm) should be performed when doubt exists.

Pathologic Subtypes

Four major subtypes, based on unique clinical features and growth patterns, categorize cutaneous melanoma. Differences in these subtypes do not influence treatment response or the durability of that response; therefore, treatment is typically based on disease staging. The four melanoma subtypes are superficial spreading, nodular, lentigo maligna, and acral lentiginous.

Abbreviations

Superficial Spreading Melanoma

Superficial spreading melanoma is the most common type of cutaneous melanoma, accounting for 70% of all melanomas. The lesions often arise from pre-existing nevi and are directly related to UV exposure. The time frame for their development is 1–5 years, often beginning with a radial (horizontal) growth phase that later progresses to a deeper vertical infiltration through the epidermis. This subtype is less common in men than in women, and the growth and development of these lesions usually occurs after puberty.

Nodular Melanoma

The second most common cutaneous melanoma, nodular melanoma, accounts for 15%–30% of all the melanomas. Nodular melanoma is generally characterized by a classical vertical growth that is extremely rapid, often developing over weeks to months. Radial growth is often absent, and the lesions often appear as symmetrical. Coloration is a uniform dark blue-black, and these melanomas are often raised over the surface of the skin in a dome-like shape. Lesions can appear at any age and are most common in men. The location of these nodules is often on the trunk, head, and neck.

Lentigo Maligna Melanoma

Generally less common than the previously mentioned subtypes, lentigo maligna melanoma accounts for 10%–15% of all cutaneous melanomas. These malignant tumors are also caused by direct UV radiation; they typically occur on the sun-exposed areas of the head, neck, and hands and are the only subtype believed to be related to cumulative sun exposure. Lentigo maligna melanomas grow less aggressively than nodular melanoma and are not as likely to metastasize. These lesions are often larger in diameter (greater than 3 mm) and are flat, tan-colored lesions with areas of dark brown or black coloration. Lentigo maligna melanomas grow slowly and lesions may take many years to be discovered. As a result, the incidence of lentigo maligna is uncommon in persons under age 50. The lesions most commonly develop on the face of elderly individuals.

Acral Lentiginous Melanoma

Although acral lentiginous melanoma is the least common melanoma in Caucasians (2%–8%), it is the most common histologic subtype seen in African Americans, Hispanics, and Asians (40%–50%). The site of origin occurs on the palms of the hands, soles of the feet, beneath the nail beds, and even on certain mucous membranes. These lesions are often rather large (greater than 3 cm), have irregular borders, and are stained dark tan or brown. The etiology of this subtype is believed to be genetically influenced rather than associated with excessive exposure to UV radiation.

Diagnosis

A complete history and physical examination should be performed on any individual who is at risk for a suspected melanoma. Total skin examination should be included, as well as a careful documentation of risk factors, particularly those associated with an increased sensitivity to the harmful effects of UV radiation. Additional diagnostic evaluations should include chest radiographs, computed topography/magnetic resonance imaging for suspected distal metastases, and hepatic enzyme profiles including lactic dehydrogenase (LDH), as these may be helpful during staging and identification of metastatic involvement.

Biopsy of the suspected tumor site is the only way to determine the pathology of a suspicious lesion (Figure 1-1). Excisional biopsies, which excise a 1–2 mm portion of surrounding normal skin and subcutaneous fat, are recommended to fully encapsulate the lesion. Shave biopsies are an inappropriate technique and should be avoided because it is important to ascertain the depth of the

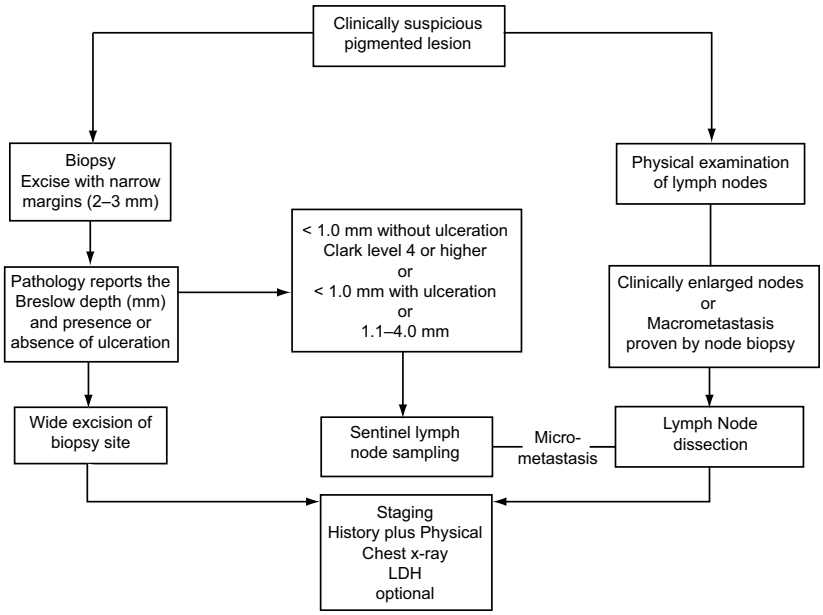

Figure 1–1. Flowchart for management of pigmented lesions.
LDH = lactic dehydrogenase.

lesional margins to appropriately stage the tumor. If excisional biopsies are impractical due to size or anatomical reasons, some type of incisional biopsy technique should be used to ensure that the deepest margin has been collected to determine invasiveness. Punch biopsies are recommended over shave biopsies for areas of skin, such as the palms of the hand or face, that are impractical for superficial marginal excision. Fine-needle aspiration is often used for enlarged lymph nodes that may be suspected of harboring melanoma. A full lymph node dissection should follow any positive findings from a nodal aspiration.

Two pathognomonic proteins most commonly used to identify melanomas are the S100 and HMB-45 proteins. The HMB-45 protein is more specific for melanoma; however, it is not always present in distantly metastasized melanomas. The S100B, one of the members of the S100 family of melanoma-specific proteins, has been useful in staging malignant melanoma, establishing prognosis, evaluating treatment outcome, and in predicting relapse. Higher levels of S100B can be indicative of metastatic growth, and decreasing S100B may reveal response to therapy. These proteins are not routinely monitored in all clinical settings and institutions, but the research supporting S100B has propagated international prospective follow-up studies of malignant melanoma to confirm and explore further the relation between serum concentrations of S100B and the course of disease.

Staging and Prognosis

Almost 3 decades ago, William H. Clark first proposed a prognostic melanoma classification system that categorized melanoma according to the level of anatomical skin penetration. Alexander Breslow improved on this system by introducing the characteristic of depth of tissue invasion through the use of direct measurement of lesion thickness. With more demonstrated prognostic significance, tumor thickness has become widely acknowledged as a superior prognostic indicator of patient survival and has proven to be less subjective than Clark's levels of classification.

The most recent American Joint Committee on Cancer (AJCC) staging system for melanoma takes into consideration the criteria of both Clark and Breslow, classifying melanoma into four stages. Whereas Clark's and Breslow's levels of classification do not account for aspects of tumor satellites and vascular invasion, the AJCC system adds these elements along with the classical tumor-node-metastasis (TNM) staging system.

Eighty-two to 85% of patients with melanoma first present with stage I or II localized disease; 10%–13% present with stage III regional disease; and the remaining 2%–5% present with stage IV distantly metastatic disease. When malignant tumors are detected at an early stage, the chance for a cure is greater. The 5-year survival rate for localized melanoma is 87%, but drops to 35% and 5% for tumors that spread to regional lymph nodes and distant organs, respectively. These statistics show that the prognosis for melanoma is largely dependent upon the stage at clinical presentation and the nodal tumor burden.

Lesion thickness is still the primary factor for tumor (T) staging for patients with stage I and II melanoma, but the number of tumor satellite metastases is now considered an important indicator of nodal (N) involvement. Tumor (T) classification no longer accounts for the level of anatomical invasion; rather, tumor thickness and the additional characteristic of ulceration, added in the most recent 2002 AJCC updates, are used to stage all patients with melanoma. The presence of ulceration in the epidermal layer over a major portion of the primary melanoma is prognostic for an increase in disease severity. The 2002 updates to the previous AJCC staging system no longer take dimensions of the nodal metastases into consideration, but rather, all patients with nodal involvement fall into a stage III classification. Tumor burden in patients with stage III disease is further characterized by clinically apparent, macroscopic, and clinically occult, microscopic, nodal involvement. Stage IV includes any patient with distant metastatic disease; prognosis is largely governed by the location of and total number of metastases. Skin and lymph nodes are obvious primary sites of metastasis, whereas lungs, liver, brain, bone, and gastrointestinal tract are considered secondary sites. The measurement of lactic dehydrogenase has also been added to the staging prognosis of a distantly metastasized tumor, and its elevation indicates greater disease progression.

These new conventions in clinical and pathological staging were incorporated as a result of recent advances in intraoperative lymphatic mapping and sentinel lymph node biopsy. Lymph node mapping aids in identifying the first or sentinel lymph node that is in direct path of lymph drainage from the primary cutaneous melanocytic lesion to better detect the extent of and natural course of the disease. In addition to TNM, Breslow's, and Clark levels of classification, primary tumor, age, and gender are also incorporated into the AJCC staging system for melanoma.

Quality Pharmaceutical Care

The general approaches for managing cutaneous melanoma are dependent on the disease stage. The risk of developing metastatic disease is directly related to the stage of initial cutaneous disease. Fortunately, the majority of melanoma lesions present themselves in earlier stages when surgical excision alone is curative. The actual excision margin is ultimately determined by tumor thickness of the primary melanocytic lesion. For melanomas that are suspected to have regional involvement, surgical excision alone may be insufficient, and additional lymphatic mapping and sentinel lymph node biopsy may be warranted.

If regional nodal involvement is suspected, as in stage III disease, adjuvant therapy with interferon-α2b, irradiation, or patient enrollment into an investigational clinical trial may also be warranted.

Management of stage IV metastatic melanoma remains controversial, with no clear-cut standard of care. Systemic chemotherapy, immunotherapy, biochemotherapy, and enrollment in investigational clinical trials are all used in treating patients with disseminated disease. Although studies of surgical resection alone in advanced disease can result in 5-year overall survival rates as high as 25%, these results are often biased by the inclusion of patients with isolated metastases. The median survival for patients with

stage IV disease with distant metastases remains at 6–10 months, with less than 5% surviving 5 years. Therefore, best supportive care and palliative radiation are reasonable options for many patients diagnosed with stage IV disease.

Treatment Plan

Nonpharmacological Treatment

Surgery

Surgical excision of localized primary melanomas is the treatment of choice and the therapeutic standard of care. It is possible to achieve cure with surgery alone in patients who present with local lesions. The excision margin is the most important determinate of cure; ensuring that the melanocytic lesion has been completely removed with certainty greatly decreases the chance of recurrence. The recommended margins of excision are determined by the tumor thickness and involve the removal of surrounding normal skin through the use of subcutaneously deep margins. Melanoma *in situ* requires a 0.5–1-cm excision around the lesion. For melanomas that are thin (less than 1 mm), a 1-cm margin is acceptable. For melanomas between 1 and 2 mm thick, most treatment centers suggest a margin of 2 cm where possible; otherwise, a minimum of 1 cm is recommended. Two trials have shown that margins of 2 cm and 5 cm were equivalent for treating melanomas of 2 mm or less. An additional trial reported a nonsignificant difference between a 1-cm and 3-cm excision margin for melanomas that were less than 2 mm thick.

The United States Intergroup Melanoma Surgical Trial confirmed that a 2-cm excision is sufficient for the removal of melanomas between 2 mm and 4 mm in thickness. Although thicker melanomas, especially those more than 4 mm thick, are associated with more severe disease and a higher risk of relapse, excising margins over 2 cm have not been found to be superior; therefore, 2 cm is considered to be the maximum margin to be used.

Because of the greater incidence for a recurring primary melanoma in those patients who have had surgical excision or other treatment for a more invasive melanoma, regular screenings should be strongly encouraged, with an annual evaluation as a minimum.

Theory supporting lymph node mapping stems from the evidence that melanoma cells spread to regionally located nodal basins via lymphatic drainage before further metastasis. Lymph node mapping is generally accomplished by an injection of a blue dye and/or radiopharmaceutical around the primary lesion, which is followed by visual or radiographic mapping to identify the sentinel, or first draining, lymph node in the lymphatic path. Lymph node mapping is recommended when isolated regional lymph nodes are clinically enlarged and palpable.

The management and dissection of clinically normal lymph nodes remain controversial. If the primary tumor's thickness is less than 1 mm, there is a low likelihood of lymph node involvement (less than 5%), and the tumor should merely be widely excised with negative margins barring any other negative prognostic factors deemed notable by the clinician. If the tumor is greater than 1 mm in thickness, there is a higher association of recurrence of the melanoma if the tumor is only excised.

Often, with the presence of clinically enlarged lymph nodes and a thicker lesion, selective lymphadenectomy of the sentinel nodes will be performed. If results from the sentinel node biopsy are positive, then full serial dissection of the remaining nodes into which the lymphatic system drains has been suggested. Several trials testing the overall survival outcome of lymph node mapping failed to show any benefit, but the advent of sentinel lymph node biopsy for staging and guiding potential therapy has solidified the use of this procedure. Some treatment centers report that sentinel lymph node mapping can correctly identify the initially affected node in 95% of patients.

Radiation Therapy

The role of radiation in treating melanoma is controversial. Resistance to radiation is common and often leads to use of high fractionated doses. The treatment of primary lesions with radiation therapy may be appropriate when taking the location into consideration. Adjuvant radiation therapy can be considered if there is extranodal extension of disease, lesions on the head and neck, incompletely excised lesions, or multiple lymph node involvement. Palliative radiation may be considered for patients with more extensive metastatic disease.

Pharmacological Therapy

As outlined above, the use of surgery alone is curative in a high percentage of cases. The use of additional treatment modalities is needed in fewer than 20% of patients at initial presentation. Adjuvant therapy is needed in patients with melanoma cases where regional and distal metastatic disease is confirmed. The effectiveness of such treatment is highly variable and objective response rates have improved little over the past 3 decades.

Adjuvant Therapy

Due to recent advances in melanoma staging, the use of adjuvant therapy in stage IIB to stage III has been gaining acceptance through the use of defined goals to reduce the incidence of recurrence. The prognosis of recurrent melanoma is dismal, and various treatment options have been studied.

Interferon-α2b remains the only drug with proven benefit as adjuvant therapy. Other treatment modalities explored for adjuvant therapy have included biochemotherapy, as well as vaccines. Many vaccine trials showed promise initially, particularly with evidence of immune activation, but none of the large randomized trials has shown any long-term clinical benefit. Randomized trials are now evaluating the value of granulocyte macrophage-colony stimulating factor as adjuvant therapy with a vaccine. An expanded discussion on vaccines is included later in this chapter under the Advanced Melanoma section. Furthermore, various chemotherapy regimens have also been tried in adjuvant settings without demonstrating significant benefit.

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Abbreviations

Interferon-α2b. Interferons, in general, consist of a group of various immunologic factors that are widely cytostatic and cytotoxic in nature. On interaction with cell surface receptors, interferons display pleiotropic pharmacological activity depending on cell type. These effects can include inhibition of cellular growth, alteration of cellular differentiation, interference with oncogene expression, and alteration in cell surface antigen expression. In addition to activating lymphocytes, interferons can further enhance cytotoxicity of target cells and increase the phagocytosis of macrophages by enhancing the overall host immune system response. Interferon-α2b has approved labeling from the FDA for use in patients with primary melanoma lesions thicker than 4 mm (stages IIB or IIC) or melanoma involving regional lymph nodes that are disease-free following surgery (stage III). Three Eastern Cooperative Oncology Group (ECOG) trials demonstrated a 20%–30% improvement in relapse-free survival with the use of interferon-α2b. Two of the three trials showed overall survival improved by as much as 30% among patients receiving high-dose interferon-α2b compared with patients in the control group.

One of the three studies showed significant improvement in 1-year relapse-free and overall survival when comparing high-dose interferon-α2b to observation in patients with stage IIB and III and T4 node-positive disease. The interferon-α2b dose was 20 million units/m^2/day intravenously for 5 of 7 days per week for 4 weeks, followed by 10 million units/m^2 given subcutaneously 3 times/week for 48 weeks. Median relapse-free survival increased by 8.9 months, and median overall survival increased by 1 year. The tolerability of this treatment was an issue for a good portion of the patients, but about 60% of patients were able to tolerate at least 80% of the recommended dose. A second study confirmed improvement in median relapse-free survival, but not in overall survival, using the same initial high-dose regimen used in the previously described study, but using a lower dose regimen (3 million units/m^2 subcutaneously for 104 weeks) for maintenance. The third study found a melanoma vaccine to be inferior compared with high-dose interferon-α2b.

There is no consistent pattern of patient response to interferon-α2b. Data to support criteria to predict which patients will respond, such as the number of positive nodes, are lacking. When considering bioimmunotherapy, the use of interferon-α2b is most practical in patients where the benefit outweighs the risk of expected and potentially intolerable toxicities. In general, these patients must have high-risk melanoma (e.g., stage IIB, IIC, or III), no serious comorbidities, and a life expectancy of more than 10 years.

As an extension of its immunomodulatory activity, interferon-α2b has many therapy-limiting adverse effects, including flu-like symptoms, fever, chills, headache, myalgias, and arthralgias, which are observed in up to 80%–90% of patients. The onset of these effects typically starts a few hours after the first injection and can last for 8–10 hours following a dose. Health care professionals who are familiar with the adverse effects of interferons should be involved in administering and managing these therapies to minimize patient discomfort through optimal supportive care. Preemptive use of acetaminophen for fever control is standard of care. Patients whose fever is unresponsive to acetaminophen may take ibuprofen to control fever, headache, and myalgia, if needed. Because flu-like symptoms can induce dehydration, empiric hydration of at least 2 L/day is critical, and must be particularly emphasized to patients who are being treated with outpatient interferon therapy. Dermatologic reactions, particularly alopecia and mild, yet transient, rash-like reactions can occur at any time during therapy.

Although the frequency and severity of adverse effects often decreases with subsequent doses, those effects, such as somnolence, confusion, mood disorders and even depression, can occur with repeated administration. They are best treated with supportive antidepressant drug therapy, typically selective serotonin reuptake inhibitors for those requiring chronic administration. Mood disorders can also be treated with valproic acid or less sedating alternatives, such as gabapentin or pregabalin.

Older patients are more susceptible to adverse effects, and fatigue is the most common dose-limiting toxicity with chronic therapy. Fatigue has been reported in 96% of patients receiving interferon, and grade III or IV fatigue in 25% of patients. Fatigue may be combated pharmacologically if other predisposing conditions of poor nutritional status, dehydration, and hypothyroidism are ruled out. Some data suggest that methylphenidate (5 mg 2 times/day with dose escalation up to 30 mg 2 times/day) is safe and effective for treating cancer-related fatigue. Selective serotonin receptor inhibitors appear to be a good option for patients whose source of fatigue may be depression secondary to interferon. However, symptomatic fatigue may be directly related to depression or interferon use. The use of corticosteroids to treat fatigue is controversial in view of the immunologic mechanisms of the antitumor effects of interferon and the chance that corticosteroids may compromise the therapy. In contrast, the progestational hormone, megestrol acetate, should not interfere with the desired interferon effects, and may be an added benefit to patients with interferon-induced anorexia. Megestrol acetate was significantly more effective than dronabinol in improving appetite and achieving weight gain. The combination of dronabinol and megestrol acetate was no more effective than megestrol acetate alone.

Most patients will require a dose adjustment due to intolerability of the interferon-α2b therapy. During induction and maintenance therapy in the three interferon trials, 28%–52% of patients had their dose modified secondary to toxicities. Dose-limiting toxicities for dose modification or interruption of therapy include granulocyte counts less than 500 cells/mm^3 or liver function tests such as AST or ALT more than 5 times the upper limit of normal.

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Interferon labeling recommends withholding the next dose of interferon-α2b until resolution to grade I or complete resolution of laboratory abnormalities (i.e, liver function tests, granulocyte count), or resuming treatment with a reduced dose. The recommendation suggests a 33% dose reduction following the first event and 66% dose reduction following the second occurrence. Based on this three-tiered dose modification, if a third event of hepatotoxicity or granulocytopenia occurs, then interferon therapy should be discontinued. In addition to these formal criteria established by ECOG, it is recommended that in the face of other laboratory abnormalities (e.g., changes in bilirubin) or an increased potential for infection or other adverse events the approach to treatment should be determined largely by the patient and treating physician, who may seek guidance from the clinical pharmacist for recommendations on dose adjustments.

In spite of its adverse reaction profile, retrospective analyses show that interferon-α2b therapy is correlated with improved quality of life-adjusted survival. Interferon-α2b is relatively cost-effective, and most patients at high-risk for recurrence of melanoma prefer this therapy, even with its adverse effect profile, to the risk of relapse. However, the response to interferon-α2b therapy is inconsistent, and the complications associated with chronic therapy are not trivial. This, coupled with the lack of survival advantage reported among the various trials, argues for better therapeutic alternatives. The survival benefit demonstrated in one clinical trial was no longer apparent when the data were analyzed at a median follow-up of 12.6 years. Another clinical trial was criticized for poor performance of the comparator vaccine. Pooled data from three studies confirmed the original results of increased relapsed-free survival, but revealed the need to develop better predictors of relapse and response to guide its use and improve the therapeutic value of interferon-α2b therapy.

Despite the data demonstrating beneficial short-term outcomes with its use, interferon-α2b is not widely accepted worldwide as a treatment modality for melanoma and its use in the United States is limited due to the chronic adverse effects profile associated with the use of larger drug doses, making it difficult to use with other treatment modalities. Some European melanoma trials have made attempts to reduce the dosage of interferon-α2b, but these studies have shown no survival advantages. Studies are ongoing to better define the optimal treatment regimen for interferon-α2b therapy in melanoma. Newer studies are attempting to determine the necessity for an intravenous induction phase followed by subcutaneous maintenance, as well as the determination of optimal dose and scheduling of interferon-α2b when it is used combination with other treatments, including adjuvant vaccines.

Vaccines. Vaccines are attractive therapy for melanoma for several reasons: 1) the known association between the development of melanoma and the activation of host humoral and cellular immune responses suggests that vaccines should possess significant activity in boosting the host immune systems to combat preexisting cancer; 2) unlike chemotherapy and bioimmunotherapy, tumor-specific vaccines should cause relatively little, if any, host toxicity. Numerous tumor-specific vaccines are in various stages of clinical development as adjuvant therapy in patients with high-risk melanoma. Adjuvant vaccine therapy has produced responses in some patients when compared with historical controls. These vaccines often encapsulate viral or mechanical lysates, or carbohydrate antigens of the melanocytic lesions to produce a host cellular and humoral response of antibody production against the tumor. Some vaccines under investigation include a GM2-ganglioside-based vaccine; a shed melanoma-antigen vaccine; M-Vax, a dinitrophenol-conjugated autologous tumor vaccine; Canvaxin, a polyvalent whole-cell vaccine; and Melacine, a melanoma-cell lysate vaccine. Despite several clinical studies that demonstrated proof of principle for vaccines in treating melanoma (characterized by T cell activation and local increases in growth factor product and secretion), their therapeutic potential has been questioned due to the limited number of objective responses noted in these trials.

Treatment of Advanced Melanoma

Treatment options for widely metastatic melanoma remain unsatisfactory, with median survival often ranging between 6 and 9 months and survival rates of only 1%–2% at 5 years. The treatment option used is an indicator of how well patients will fair; rather, the extent and aggressive nature of their disease is a better predictor of survival. Cytotoxic chemotherapy and immunotherapy, used alone or in combination, are the major systemic treatment options for patients who have metastatic disease. This section focuses on the clinical experience reported with chemotherapy given as single drugs, in combination chemotherapy regimens, or in combination with interleukin-2 (IL-2) and/or interferon-α2b in a biochemotherapy regimen. Managing toxicities and complications secondary to highly cytotoxic or immunomodulatory chemotherapy is a primary responsibility of clinical pharmacists. Implementation of an appropriate toxicity screening and supportive care plan for both single-agent and combination regimens will be outlined. Although the clinical use of interferon-α2b and IL-2 therapies for metastatic melanoma is discussed here, a more detailed rationale for immunotherapy was discussed in the Adjuvant Therapies section.

Single-Agent Systemic Chemotherapy. Active traditional cytotoxic drugs, used as monotherapy chemotherapy for melanoma, have variable response rates

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(at most 10%–25%). The various classes of chemotherapeutic drugs tested for the treatment of metastatic melanoma include dacarbazine (DTIC), nitrosoureas, taxanes, platinum drugs, and vinca alkaloids. All have been studied and used clinically with inconsistent results. In general, responses to these drugs are brief in duration, rarely lasting more than several months, and these drugs used systemically result in less than 5% complete responses. Patients who benefit the most are asymptomatic and have smaller volume metastases in the skin, lymph nodes, and lungs.

Dacarbazine. The most active drug, and the only chemotherapeutic drug that has FDA-approved labeling for treating advanced melanoma, is DTIC, which produces overall response rates of 10%–20% and complete remissions in up to 5% of patients. Long-term remissions are achieved in about 25% of complete responders, but fewer than 2% of all patients are expected to survive 6 years.

Dacarbazine is an imidazole carboxamide purine analog that acts as an alkylating drug to presumably inhibit DNA synthesis. Major adverse effects of DTIC are generally limited to nausea and vomiting, combined with anorexia, which has been reported in 90% of treated patients subsequent to their initial dose. Onset of emesis is typically 2–6 hours after administration, and may last up to 24 hours. The high emetogenic potential of DTIC lessens characteristically with each subsequent dose, but pretreatment with a 5-hydroxytryptanine type 3 receptor ($5\text{-}HT_3$) antagonist plus aprepitant, plus a corticosteroid is recommended to prevent acute emesis. Delayed emesis should be countered with oral aprepitant and dexamethasone. Bone marrow suppression is typically modest and manageable, as are fatigue and alopecia.

Treatment schedules typically differ by the number of days of administration. The three standard dosing regimens for DTIC in melanoma therapy are 850–1000 mg/m^2 intravenously on only day 1; 200–250 mg/m^2 intravenously on days 1–5; and 4.5 mg/kg/day intravenously on days 1–10 each repeated every 21–28 days. No studies have demonstrated greater responses with any of the differing schedules of single-agent DTIC, but the 1-day regimen allows for a more facile approach to treating patients in an outpatient setting. This approach for single-day administration becomes preferable for reasons of cost and convenience, especially as more effective antiemetic drugs allow patients to tolerate the highly emetic nature of large single high-doses of DTIC. Because DTIC is an irritant and may cause tissue damage, extravasation precautions should be used. If venous pain occurs along the injection site following rapid intravenous injection, dilution and a slower administration rate should be used. The application of ice to the injection site may also be helpful.

Temozolomide. Temozolomide, an orally bioavailable prodrug of DTIC, is being extensively studied for treatment of advanced metastatic melanoma. Approved for malignancies of the central nervous system, temozolomide is an imidotetrazine derivative that at physiologic pH, spontaneously converts to 3-methyl-(triazen-1-yl) imidazole-4-carboxamide, the active metabolite of DTIC. One Phase III trial compared temozolomide (200 mg/m^2/day orally for 5 days every 28 days) with DTIC (250 mg/m^2/day intravenously for 5 days every 3 weeks) in 305 patients who did not have brain metastases. Similar response rates (13.5% vs. 12.1%) were reported for both drugs; although not statistically significant, there were trends toward improved overall survival (7.9 vs. 5.7 months) with the temozolomide arm.

Temozolomide also produced an apparent improvement in median progression-free survival (1.9 vs. 1.5 months), health-related quality of life, and fewer central nervous system relapses relative to DTIC. Treatment-emergent events were similar in both groups along with a similar percentage reporting grade III or IV adverse events. Pain was reported more often in the DTIC group than in the temozolomide group (13% vs. 7%). Nausea and vomiting also occurs in up to 75% of patients, but much like DTIC, this effect subsides with subsequent dosing. Clinical pharmacists should recommend antiemetic precautions for temozolomide that mimic those used for DTIC. Regardless of the ease of oral administration and potentially more manageable toxicity profile compared with DTIC, the FDA Oncologic Drugs Advisory Committee did not find the clinical data sufficiently compelling to approve temozolomide to treat metastatic melanoma.

Temozolomide research is ongoing to identify novel dosing schedules and combinations, particularly in patients with metastatic melanoma who may have central nervous system complications. Clinical trials using temozolomide in combination with thalidomide, with or without whole-brain radiation therapy, have shown synergy in patients treated for stage IV melanoma with central nervous system metastases.

Nitrosoureas. Currently available nitrosoureas in the United States include carmustine and lomustine. Fotemustine is a chloroethyl nitrosourea that is widely used in other countries, but is not currently available in the United States. These drugs are alkylators that are capable of inhibiting DNA and RNA synthesis by inhibiting essential enzyme reactions involved in DNA synthesis. The nitrosoureas are considered to have cell cycle nonspecific activity, but appear to slow the progression of the malignant cell from the S to the G2 phase and arrest cellular progression through the G2 phase.

The response rates to nitrosoureas in the treatment of metastatic melanoma are similar to that of DTIC, ranging from 10% to 20%. Carmustine is the most widely studied nitrosourea for metastatic melanoma, both as a single drug and in combination therapies. The recommended carmustine dose, as a single infusion is 150–200 mg/m^2 in untreated patients; patients previously exposed to DTIC are less likely to respond to carmustine and may require a higher dose than untreated patients. Melanoma resistance to alkylators such as nitrosoureas has been proposed to be a result of increased endogenous production of glutathione. The combination of

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carmustine with high-dose acetaminophen, to deplete intracellular glutathione, with *N*-acetylcysteine rescue has been used as an attempt to overcome resistance. Dose-escalation using this strategy is ongoing in Phase I clinical studies.

Nausea and vomiting are usually delayed in onset by 2–4 hours, but may last up to 4–6 hours, often requiring antiemetic therapy. Myelosuppression is the main dose-limiting toxicity as depression in blood counts, particularly platelets, is typically prolonged. Due to delayed and cumulative hematologic toxicity, a course of carmustine should not be repeated any sooner than 6 weeks. Blood counts should be monitored weekly. Pulmonary toxicities are the second most notable dose-limiting toxicity, with patients receiving a cumulative dose greater than 1400 mg/m^2 at significantly higher risk. This toxicity usually manifests within 3 years of therapy, and the incidence ranges from 20% to 30%. Fatalities related to pulmonary toxicity have occurred, and cases of delayed-onset pulmonary fibrosis have been reported up to 17 years after treatment with carmustine. Alopecia is more severe with nitrosoureas than with DTIC. Other adverse effects may include dizziness, ataxia, ocular toxicity, kidney failure, and hyperpigmentation.

The dilution technique when reconstituting carmustine for infusion is an important consideration for pharmacists. The limited stability of carmustine requires that the powder be initially diluted with an absolute alcohol diluent, which is provided with each vial of carmustine. Once reconstituted, the initial carmustine solution has a final alcohol concentration of 10%. Further dilution in 250-ml or 500-ml containers is required. Injectable carmustine must be dispensed only in glass bottles or non-polyvinyl chloride-containing bags, as it is capable of significant adsorption to polyvinyl chloride. Burning and significant vein irritation may develop during infusion because of the alcohol content. Clinical pharmacists can instruct the nursing staff to evaluate patients for signs of irritation at the infusion site. Furthermore, clinical pharmacists can educate patients regarding the potential for vein irritation and for which symptoms to report. Patients also require education regarding the potential for a disulfiram-like reaction. Drugs such as metronidazole, which can precipitate disulfiram-like reactions, should be discontinued for a minimum of 2–3 days before initiating nitrosourea therapy.

Platinum Anticancer Drugs. Single-agent activity of platinum anticancer drugs, such as cisplatin and carboplatin, in patients with metastatic melanoma has been modest. Cisplatin has been used more extensively than carboplatin in the treatment of advanced melanoma, with modest response rates of 10%–20%. The platinum compounds, classified as cell-cycle nonspecific alkylators, react with nucleophilic sites on DNA, RNA, or protein resulting in the formation of bifunctional covalent links. The inter-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis. The adverse effects of the platinum anticancer drugs are significant, and the resultant activity reported against metastatic melanoma in clinical trials is often overshadowed by the considerable morbidity associated with treatment.

The overall adverse effect profile of cisplatin is much more debilitating than that of carboplatin. The most notable dose-limiting toxicities of cisplatin are nephrotoxicity and neurotoxicity that occur with higher cumulative doses. Damage to the kidneys is most significant as it occurs in 28%–36% of patients who receive even an initial low dose (50 mg/m^2) of cisplatin. The damage is cumulative and to some degree irreversible. Pharmacists can play an important role in monitoring indicators of kidney damage (e.g., creatinine clearance, serum creatinine, and blood urea nitrogen), as well as ensuring that orders for adequate hydration are written for patients before drug administration. Pharmacists should review patients' kidney function before subsequent dosing of cisplatin therapy. If kidney function has not returned to normal, additional doses of platinum therapy will potentially cause more severe damage and prolong nephrotoxicity. Hydration with normal saline at a rate of 150–200 mL/hour before, during, and up to 8 hours after administration of cisplatin can help promote intratubular flow through the nephrons and decrease kidney injury. Administration of mannitol can be used to promote diuresis. Pharmacists should also ensure that cisplatin is not administered at an infusion rate greater than 1 mg/kg/hour. Pharmacists should ensure that concurrent nephrotoxic drugs are being withheld while patients are receiving therapy.

Peripheral neuropathy is the second most notable dose-limiting toxicity of cisplatin therapy, often occurring with cumulative doses of 300–600 mg/m^2. The features of neuropathy are uniform and consistent with damage primarily to large sensory fibers; numbness and tingling are usually the first symptoms, followed by an impaired sense of joint position and sensory ataxia. Although the toxicity is considered reversible, symptoms of this condition can persist up to 1 year or more. Vitamin E supplementation of 300 mg/day prior to therapy for up to 3 months post-infusion has reduced some of the peripheral neuropathy. Ototoxicity and tinnitus are often irreversible, dose-related toxicities experienced by 31% of patients following initial doses. Myelosuppression can also be significant, occurring in 25%–30% of patients, with platelets and leukocytes nadirs occurring 18–23 days after therapy and recovering after about 39 days. Pharmacists should monitor electrolyte concentrations closely, and recommendations for supplementation should be aggressive. One study showed that single-agent cisplatin doses up to 150 mg/m^2 in combination with the bone marrow and kidney chemoprotective drug, amifostine, produced tumor responses in 53% of patients with metastatic melanoma. However, the duration of response did not last beyond 4 months, and there were no complete responders to treatment. Further studies with and without amifostine showed activity, but differences in both response and toxicity were not statistically significant.

Treatment approaches for highly emetogenic chemotherapy are discussed in detail in the Supportive Care of the Cancer Patient chapter. The highly emetogenic nature of cisplatin suggest that patients receiving any amount of the drug require prophylaxis. Vomiting typically begins 1-6 hours after administration, and can last 120 hours or more. Treatment can include a 5-HT$_3$ antagonist of choice,

such as ondansetron 8-24 mg given intravenously before chemotherapy, plus aprepitant at an initial dose of 125 mg orally 1 hour before chemotherapy, and 80 mg on days 2 and 3 post-treatment. Dexamethasone 12 mg intravenously or orally should be given before chemotherapy, then 8 mg/day for 3 additional days. The clinical data leading to aprepitant's approval only evaluated a single day of highly emetogenic chemotherapy (predominantly cisplatin). It is also approved for moderately emetogenic chemotherapy, but again was studied with regimens administering chemotherapy on a single day (predominately AC for breast cancer). Consequently, there are no data to guide therapy for multiple daily doses of highly emetogenic therapy. Aprepitant has been shown to be safe when administered daily for weeks in antidepression trials; however, its efficacy for chemotherapy-induced nausea and vomiting with dosing beyond 3 days is not established. There are no data suggesting it is effective for patients with established nausea and vomiting, or for as-needed use.

In contrast to the adverse effect profile of cisplatin, the dose-limiting toxicity of carboplatin is myelosuppression. Myelosuppression caused by carboplatin, particularly thrombocytopenia seen in about 25% of patients, is dose-related and reversible. With single-agent therapy, the nadir for platelets is usually 21 days. The risk of severe myelosuppression, as well as other adverse events, is increased in patients who previously received cisplatin and/or radiation therapy. Other risk factors include combination with other myelosuppressive drugs, low initial blood cell counts, increasing age, kidney dysfunction, poor performance status, or extensive prior chemotherapy. Evidence also supports the use of amifostine administered 15 minutes before carboplatin infusions and 2 hours after the end of administration to counter the decrease in platelet counts. Abnormalities in liver or kidney function as indicated by elevations in liver enzymes or markers of kidney dysfunction may occur, as well as electrolyte wasting, alopecia, and pain at the injection site. Some institutions consider platinum anticancer drugs to be vesicants, and extravasation precautions for patients receiving either carboplatin or cisplatin should be used. Furthermore, although the emetogenic potential of carboplatin is not as severe as cisplatin (65% vs. 100%), pharmacists should ensure that patients receive prophylactic antiemetic drugs and antiemetic drugs for delayed nausea, which can last for up to 48 hours. Single-agent carboplatin in doses of 400 mg/m^2, given intravenously every 4 weeks to patients with advanced melanoma, has a demonstrated response rate in the range of 16%–19%, with a majority of those being partial responses.

Taxanes. The more active cytotoxic drugs used for treating metastatic melanoma have been those drugs that interfere with the microtubule disassembly of cells, such as the taxanes. Paclitaxel and docetaxel have shown overall response rates of 3.3%–17% when used as single drugs. Promising results suggest that taxanes could be potential second-line cytotoxic drugs in patients who have disease progression following first-line chemotherapy. The median duration of response is variable from 9 to 14 months, with case reports of long durable responses extending to 2–3 years. The most notable toxicity associated with the taxanes is neutropenia, which is severe but transient, with the nadir occurring after 5–8 days and rapidly recovering. Single-agent studies with 100 mg/m^2 of docetaxel every 3 weeks showed significant grade IV neutropenia in up to 92% of patients; 49% required hospitalization for the management of neutropenic fever. Pharmacists should be well aware of this adverse effect and be prepared to initiate neutropenia precautions with the proper use of antibiotic drugs and colony-stimulating factors. Docetaxel induces generalized alopecia in up to 83% of patients, and mild to moderate hypersensitivity reactions have been reported in 42% of patients. Dexamethasone administered the day prior, day of, and day after docetaxel is used to decrease the risk of fluid retention/capillary leak that occurs with large cumulative doses.

A dose-intensive regimen of paclitaxel using 200–300 mg/m^2 infused over 24 hours with or without granulocyte colony-stimulating factor support was first used in Phase I trials. Subsequent Phase I/II studies administered paclitaxel on a weekly schedule of 150 mg/m^2 over 1 hour every week for 6 weeks in repeated 8-week cycles after this regimen was proven effective and tolerable in metastatic breast and lung cancers. One study reported two partial responses in 15 patients who progressed following first-line cytotoxic therapy, indicating the potential usefulness of paclitaxel as second-line therapy. Grade III–IV hematologic toxicities were reported in 25% of patients. One other Phase II study of single-agent paclitaxel in melanoma showed that 3 out of 5 patients who had partial responses had failed on previous therapy with a combination regimen of cisplatin, vinblastine, DTIC, interferon-α2b, and IL-2. The results suggest a lack of cross-resistance between regimens. The adverse effects of paclitaxel administered in this study were mild, manageable, and mostly reversible.

Additional grade III–IV adverse effects expected in patients receiving taxanes include diarrhea, stomatitis, fatigue, mucositis, hypersensitivity reactions, and fluid retention. Arthralgias and myalgias occur in 20%–30% of patients and, although dose-related, are reversible. However, long-lasting peripheral neuropathy may persist months after therapy cessation.

The emetic potential of the taxanes is intermediate, and although pretreatment with dexamethasone 4–8 mg orally given before administration is warranted, there are no additional guidelines for using antiemetic drugs for delayed emesis. Paclitaxel and docetaxel are also vascular irritants and should be labeled accordingly to alert the nursing staff and other health care providers of proper administration and precautions.

Other Single-Agent Chemotherapies. Investigational therapies of single-agent compounds showing promise against metastatic melanoma include a new class of non-taxane tubulin polymerization drugs known as epothilones. Tumor responses are reported in patients who have metastatic melanoma, and have prompted the initiation of an epothilone B-analog into Phase II trials in patients with cytokine-resistant tumors. An investigational, orally

Gogas H, Bafaloukos D, Bedikian AY. The role of taxanes in the treatment of metastatic melanoma. Melanoma Res 2004;14:415–20. Review.

administered, lipid-soluble dihydrofolate reductase inhibitor, piritrexim, has also produced promising results in treating refractory metastatic melanoma patients.

Combination Chemotherapy. Melanoma remains one of the most chemotherapy-resistant solid tumors. As a whole, when compared with single-agent therapy, the response rates for multidrug chemotherapeutic regimens were marginally increased (30%–50%), although there has been no discernible or significant difference in overall survival rates, and the likelihood of adverse effects was significantly greater with combination therapy. Patients with good performance status, less than age 65, no prior chemotherapy, normal hepatic and kidney function, and those with the absence of central nervous system metastases will potentially be able to withstand the higher incidence of adverse effects experienced with combination regimens.

Nitrosourea and DTIC-Based Combination Therapies. Combinations of a nitrosourea with DTIC have been extensively studied in the form of two particular regimens: carmustine, hydroxyurea, and DTIC (BHD) and bleomycin, vincristine, lomustine, and DTIC (BOLD). In the BHD regimen, carmustine is given 150 mg/m^2 intravenously on day 1 every 8 weeks, hydroxyurea is given 1500 mg/m^2 orally on days 1–5 every 28 days, and DTIC is administered as a 150 mg/m^2 intravenous dose on days 1–5 every 28 days. Hydroxyurea is considered a cell-cycle specific drug effective in the S-phase of cell division and inhibits the conversion of ribonucleotide diphosphates to deoxyribonucleotides through inhibition of ribonucleotide reductase. Response rates for the BHD regimen in Phase II–III trials have ranged from 27% to 31%, but overall survival was not improved.

The BOLD regimen consists of bleomycin 7.5 units subcutaneously on the first course and 15 units in subsequent cycles, administered on days 1 and 4; vincristine 1 mg/m^2 intravenously on days 1 and 5; lomustine 80 mg/m^2 orally on day 1; and DTIC 200 mg/m^2 intravenously on days 1–5. The entire cycle is repeated every 4–6 weeks. Initial results boasted a 40% response rate, but subsequent studies showed that overall response rates ranged from 4% to 20%, suggesting that this combination regimen is not superior to other less toxic drug regimens. The BOLD regimen is still actively used in patients with uveal melanoma, a malignancy clinically distinct malignancy from cutaneous melanoma that accounts for about 5% of all melanomas. The lack of significant single-agent activity against cutaneous melanoma makes hydroxyurea and bleomycin questionable contributors in the activities of either of these regimens for advanced disease.

Taxane-Based Combination Therapy. Combinations of taxanes with DTIC, temozolomide, platinum compounds, or tamoxifen have demonstrated response rates ranging 12% to 41%. These response rates suggest efficacy equal to various other cytotoxic combination regimens, with the most encouraging results produced when taxanes are incorporated as second-line drugs for the treatment of advanced melanoma. Objective response rates of 24% have been achieved with the combination of docetaxel (80 mg/m^2 given intravenously on day 1) with DTIC (400 mg/m^2 given intravenously on days 1 and 2) administered every 21 days. Complete response rates were reported in metastatic sites such as the lymph nodes, soft tissue, and the lung for 7% of patients receiving this regimen. The highest response rates were observed in the subcutaneous, skin, and lymph node metastatic disease rather than in visceral sites. Median survival was 10 months. The dose-limiting toxicity of docetaxel-containing regimens is bone marrow suppression; however, lowering the docetaxel dose in this combination regimen reduced the incidence of grade III–IV neutropenia to 20%. Further dose escalation of DTIC in subsequent Phase I/II trials (maximum tolerated dose of 850 mg/m^2 as a single intravenous dose) with the same 80 mg/m^2 dose of docetaxel did not improve response.

Similar overall response rates and a 16-month median survival were achieved in a Phase II trial of docetaxel with temozolomide (150 mg/m^2 given orally on days 1–5) that supported the potential for this marginally less myelosuppressive regimen. Of interest, 3 out of 8 patients with central nervous system metastases achieved an objective response lasting 5, 6, and 12 months.

Paclitaxel has also been evaluated in a variety of combination regimens. In a Phase II study of paclitaxel combined with DTIC, paclitaxel doses of 250 mg/m^2 with DTIC doses of 1000 mg/m^2 given intravenously on day 1, were well tolerated with little myelosuppression or other toxicities reported. Three out of 25 (12.5%) patients responded, and for patients who had no previous systemic therapy, the response rate was 20%; the overall response rate for this combination was no greater than that observed for single agent therapy. A response rate of 20% has also been reported for the combination of paclitaxel (175 mg/m^2 infused over 3 hours) and carboplatin using the Calvert equation (area under the curve 7.5 mg/mL x minute). Another study combined paclitaxel (225 mg/m^2 intravenously over 3 hours every 3 weeks) and tamoxifen 40 mg/day orally, yielding 18% responses in patients who had previously been treated with DTIC-based combination chemotherapy. A Phase II study combining paclitaxel along with cisplatin and DTIC was shown to have a 41% response rate in 46 patients treated with this regimen. Replacing vinblastine with paclitaxel in the cisplatin, vinblastine, and DTIC (CVD) regimen yielded a median overall survival of 11 months, ranging from 1.5 to 36 months. In summary, taxane combination regimens, although promising as second-line therapy, have not yielded activity superior to single-agent therapy.

Cisplatin-Based Combination Therapy. Combination therapies using cisplatin and DTIC are some of the most active regimens studied in metastatic melanoma. The two-drug regimen of cisplatin and DTIC, the combination therapies of CVD, and the Dartmouth four-drug regimen (Table 1-2) have all been extensively studied. Response rates varying between 17% and 53% have been reported for patients treated with the two-drug regimen of cisplatin 50 mg/m^2/day plus DTIC 350 mg/m^2/day given intravenously for 3 days. An initial study of the CVD regimen (consisting of cisplatin 20 mg/m^2 on days 1–4, vinblastine 2 mg/m^2 on days 1–4, and DTIC 800 mg/m^2 on day 1, all given intravenously and repeated every 3 weeks) has produced responses in 40% of patients, with a median overall survival of 9 months. Subsequent studies have not supported these initial promising results, with most studies

Table 1-2. Melanoma Chemotherapy Regimens and Associated Adverse Events

Regimen/Number of Patients	Drug Dose and Route	Grade III–IV Toxicities		Consequences of Adverse Event(s)
Cisplatin Dacarbazine Interferon-α2b Interleukin-2 N = 44	Cisplatin 25 mg/m²/day IV over 1 hour days 1–3, followed immediately by DTIC 250 mg/m²/day IV over 30 minutes days 1–3 IFN-A2B 5 MU/m²/day SQ days 6, 8, 10, 13, and 15 IL-2 18 MU/m²/day IV days 6–10 (Monday-Friday) and days 13–15 of each treatment cycle Repeat cycle every 28 days	Neutropenia[a] Leukopenia[a] Thrombocytopenia[a] Anemia[a] Nausea[a] Vomiting[a] Anorexia[a] Fatigue[a] Transaminases[a] Nephrotoxicity[a]	23% 6% 6% 2% 9% 9% 5% 3% 3% 1%	No hospitalizations were required for neutropenic fever or infection 13 dose reductions (treatment cycles 2–6) for toxicity Two deaths possibly related to treatment Corticosteroids were omitted from this regimen, potentially accounting for the high incidence of Grade III–IV emetogenic toxicities
CVD N = 50	Cisplatin 20 mg/m²/day IV days 2–5 Vinblastine 1.6 mg/m²/day IV days 1–5 DTIC 800 mg/m²/day IV day 1 Repeat cycle every 21 days	Neutro-/Leukopenia Grade IV Neutropenic Fever Thrombocytopenia Nausea/Vomiting[b] Renal[b] Diarrhea[b] Hypomagnesemia Neuropathy	 50% 30% 26% 86% 12% 34% 68% 20%	Hospitalization 10% Treatment was discontinued in 6% of patients due to renal toxicity Dose-limiting toxicity was peripheral neuropathy
Dacarbazine (1-day Regimen) N = 121	DTIC 10,000 mg/m² IV day 1 Repeat cycle every 21 days	Neutropenia Grade III Grade IV Leukopenia Thrombocytopenia Anemia Nausea/Vomiting Dyspnea	 10% 9% 1% 7% 6% 5% 1%	Three patients removed from the study for toxicity
Dacarbazine (5-day Regimen) N = 149	DTIC 250 mg/m²/day IV over 30 minutes days 1–5 Repeat cycle every 21 days	Neutropenia Anemia Thrombocytopenia Pain[c] Nausea/Vomiting[c] Constipation[c] Fever[c] Headache[c] Fatigue[c] Somnolence[c] Asthenia[c]	2% 1% 8% 13% 8% 3% 2% 1% 1% 1% 1%	Delayed cycles 6% Discontinuation secondary to adverse events 5% No toxic deaths Dose reductions in 2% of cycles
Dacarbazine Carmustine Cisplatin Tamoxifen With tamoxifen: N = 101 Without tamoxifen N = 98	DTIC 220 mg/m²/day IV days 1–3, and days 22–24 Carmustine 150 mg/m²/day IV day 1 Cisplatin 25 mg/m²/day IV days 1–3, and days 22–24 Tamoxifen 160 mg/day PO 7 days before chemotherapy, then 40 mg/day on days 1–42 Repeat cycle every 43 days	Neutropenia[d] without tamoxifen with tamoxifen Neutropenic fever Thrombocytopenia[d] Deep vein thrombosis Vomiting Infection Hot flashes[c] With tamoxifen Without tamoxifen	 31% 32% 5% 43% 6% 40% 2% 3% 1%	Toxic mortality 1% Hemorrhage requiring transfusion 9.5%

Table 1-2. Melanoma Chemotherapy Regimens and Associated Adverse Events (Continued)

Regimen/Number of Patients	Drug Dose and Route	Grade III–IV Toxicities		Consequences of Adverse Event(s)
Dacarbazine Cisplatin Vinblastine Interferon-α2b Interleukin-2 N = 44	DTIC 800 mg/m^2 IV day 1 Cisplatin 20 mg/m^2/day IV days 1–4 Vinblastine 1.2 mg/m^2/day IV days 1–4 IFN-α2b 5 MU/m^2/day SQ days 1–5, 8, 10, and 12 IL-2 9 MU/m^2/day IV continuous infusion days 1–4 Filgrastim 5 mcg/kg/day SQ days 7–16 Repeat cycle every 21 days for a maximum of four cycles	Neutropenia[d] Neutropenic fever Infection Thrombocytopenia Hypotension Nausea/vomiting Renal insufficiency Neurologic toxicity Bleeding	30% 9% 7% 43% 30% 27% 11% 5% 2%	34% of patients required delay in discharge or readmission for febrile neutropenia or dehydration secondary to nausea and vomiting Prophylactic antibiotic drugs, antipyretics, antipruritics, and H_2-blockers were used A maximum of four cycles were administered
Dartmouth Regimen N = 119	Tamoxifen 10 mg PO twice daily (start 1 week before chemotherapy and continue indefinitely) Carmustine (BCNU) 150 mg/m^2 (repeat every 42 days, every other cycle) Cisplatin 25 mg/m^2/day IV days 1–3 DTIC 220 mg/m^2/day IV days 1–3 Repeat cisplatin, DTIC every 21 days	Neutropenia Leukopenia Anemia Thrombocytopenia Nausea/vomiting Fatigue Dyspnea Increased serum creatinine	39% 9% 32% 57% 18% 7% 5% 3%	25 patients removed from the study for toxicity

[a]Percentage of cycles.
[b]Grade unknown.
[c]Grade III.
[d]Grade I.
CVD = cisplatin, vinblastine, and dacarbazine; DTIC = dacarbazine; H_2 = histamine receptor 2; IFN = interferon; IL - interleukin; IV = intravenously; PO = orally; SQ = subcutaneously.

demonstrating that the CVD regimen is not superior to single-agent DTIC treatment. The CVD regimen was considered to have a higher incidence of grade III–IV toxicities, including leukopenia/neutropenia (50%), neutropenic fever (30%), thrombocytopenia (26%), and dose-limiting peripheral neuropathy (20%), than single-agent DTIC regimens. The CVD regimen resulted in hospitalizations in 10% of patients, and treatment was discontinued in 6% of patients due to kidney toxicity.

The Dartmouth regimen combined cisplatin 25 mg/m^2 given intravenously on days 1–3 every 3–4 weeks; DTIC 220 mg/m^2 intravenously on days 1–3 every 3–4 weeks; carmustine 150 mg/m^2 intravenously on day 1 every 6–8 weeks; and tamoxifen 10 mg 2 times/day orally continuously starting 1 week before chemotherapy. Initial Phase II studies with the Dartmouth regimen reported response rates as high as 46%, with a fourth of these responses being complete. When tamoxifen was removed from this regimen, response rates fell to 10% in subsequent studies. Unfortunately, follow-up studies did not confirm these exciting initial results because response rates varied in the range of 13% to 26%. Further studies comparing the Dartmouth regimen to either DTIC alone or in combination with interferon-α2b produced response rates of 15%, with overall survival extending to only 7 months. The grade III–IV toxicities of the Dartmouth regimen forced 21% of patients to be removed from the study due to excessive myelosuppression, with 57% experiencing thrombocytopenia and 32% experiencing anemia. As with single-agent cisplatin, the presence of this highly emetogenic drug in both the Dartmouth regimen and CVD requires adequate prophylaxis for acute and delayed nausea and vomiting. Currently, no convincing evidence supports the use of combination chemotherapy, rather than DTIC or any other single drug alone, in patients with advanced melanoma.

Tamoxifen-Based Therapy. The clinical activity of tamoxifen in melanoma has been examined since the presence of estrogen receptors was demonstrated in metastases of human melanoma. Single-agent tamoxifen for advanced melanoma has yielded response rates of less than 10%, but benefits have been reported when combined with cytotoxic chemotherapy regimens. Of six clinical trials comparing a variety of chemotherapy-based regimens with and without tamoxifen, only one study, single-agent DTIC with tamoxifen, showed a demonstrable improvement in response rate and survival. Response increased from 12% to 28%, and median survival from 23 weeks to 41 weeks in the tamoxifen group. It is unclear whether certain patient subpopulations may benefit from the addition of tamoxifen to their regimens, but women seemed to achieve a greater benefit in survival compared with men (69 vs. 31 weeks) in this sole supporting study. The survival advantage observed in this trial was confined to women and the effect size was modest. The remaining clinical evidence from several large multicenter trials comparing the addition of tamoxifen to multidrug regimens with or without interferon-α2b therapy has demonstrated no advantage in adding tamoxifen to

Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol 1999;17(9):2745–51.

metastatic melanoma therapy. A recent meta-analysis of the published, randomized, controlled trials also failed to demonstrate evidence of the benefit from tamoxifen-containing regimens in the treatment of patients with malignant melanoma.

In addition, the recent development of more specific immunohistochemical approaches of identifying estrogen receptor binding suggests that earlier studies identifying specific estrogen receptor expression in melanoma were flawed.

Single-Agent Immunotherapy. Interferon-α2b produces response rates of 15% as a single drug when used in patients with stage IV metastatic melanoma. The best responses to interferon-α2b therapy were seen in patients with small volume, non-visceral metastasis. Interleuken-2 (aldesleukin) is the only other biological drug that demonstrated activity against metastatic melanoma. Interleukin-2 has a single-agent response rate that is slightly better than interferon-α2b (20% vs. 15%) and has FDA-approved labeling for treating metastatic melanoma, whereas interferon-α2b does not.

Interleukin-2. Interleukin-2 is a naturally produced cytokine released by lymphocytes that is produced for clinical use using recombinant DNA technology. Early laboratory models correlated tumor response with dose intensity, and so the regimen of 600,000–720,000 IU/kg/dose given intravenously every 8 hours became known as high-dose IL-2. Although the exact mechanism by which IL-2 exerts its antitumor effects is largely unknown, the immunomodulatory role of IL-2 is thought to enhance the patient's immune system to elicit an attack against the melanoma tumor. The activities of IL-2 include enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human IL-2-dependent cells; enhancement of lymphocyte cytotoxicity; induction of lymphokine-activated killer cell and natural killer cell activity; and induction of the production of other cytokines such as interferon-γ, IL-1, and tumor necrosis factor. Aldesleukin (Proleukin) is the only commercially available IL-2 in the United States; however, several other IL-2 products have been studied in investigational clinical trials. Because many investigational IL-2 products have been used in clinical studies and others are available outside of the United States, standardization of IL-2 doses, based on activity units, normalizes the dosing of IL-2. An important note for pharmacists who work with multiple IL-2 products in various investigational protocols is that one unit of aldesleukin is equal to 6 IU of IL-2.

The majority of clinical trials have used high-dose IL-2 consisting of 600,000–720,000 IU/kg intravenously every 8 hours for 14 dosages, which was then repeated cyclically following 9-day rest periods.

Like interferon-α2b, the adverse effect profile for IL-2 is extensive and includes flu-like symptoms, vascular leak syndrome, cardiovascular complications, myelosuppression, neurotoxicity, gastrointestinal effects, kidney dysfunction, hypothyroidism, and rash. Hepatotoxicity can also occur, but is typically reversible with normalization of hepatic indices within 4–6 days after discontinuation of therapy.

Patients receiving these therapies should be hospitalized and provided specialized supportive care, premedication with acetaminophen and diphenhydramine, as well as the attention of experienced clinicians familiar with the administration of biotherapies. Due to possibility of multiorgan toxicities occurring during the treatment interval, patient selection for IL-2 therapy is important. Regardless of the relatively low percentage of patients who respond, for those who do the response seems to be durable, often lasting more than 5 years in some patients. The combination of these biological therapies with melanoma-specific vaccines and gene therapy for metastatic disease is now under investigation.

Combination Biochemotherapy. Biochemotherapy refers to the combination of cytokines, particularly interferon-α2b and IL-2 with chemotherapy. In hopes of improving the still dismal overall survival rates for advanced melanoma, an enormous amount of research studying the effectiveness of combining biological agents and cytotoxic compounds has been undertaken. The basis for these trials has been developed rationally from preclinical studies that suggest some degree of synergy with the combination of drugs known to be active when used singly.

Interferon-α2b-Based Biochemotherapy Regimens. The addition of interferon-α2b to single-agent cytotoxic chemotherapy has been disappointing, showing activity similar to the single agent used alone for drugs such as DTIC, cisplatin, vinca alkaloids, or nitrosoureas. Combination chemotherapy regimens using multidrug cytotoxins, such as CVD or the Dartmouth regimen, with added interferon-α2b therapy have also shown minimal benefit compared with the multidrug chemotherapy regimen alone. One of the first positive studies used interferon-α2b added to the BOLD regimen. Initial reports suggested an overall response rate of 63% (13% complete responses), but subsequent studies showed that overall response rates slipped to only 33%. With the exception of one other promising study demonstrating a 53% overall response rate in patients receiving both DTIC and interferon-α2b compared with 18% of those treated with DTIC alone, the collective data from all other trials suggest that the addition of interferon-α2b to drugs such as DTIC does not increase response or enhance survival. Therefore, the addition of interferon-α2b to chemotherapy for metastatic melanoma cannot be recommended as it produces no significant benefit on survival and only increases treatment-related toxicity.

Interleukin-2-Based Biochemotherapy Regimens. Interleukin-2 treatment with various cytotoxic drugs has produced mixed results. The combination of IL-2 with DTIC has resulted in considerably more toxicity than

Lens MB, Reiman T, Husain AF. Use of tamoxifen in the treatment of malignant melanoma: systematic review and metaanalysis of randomized controlled trials. Cancer 2003;98(7):1355–61.

Komenaka I, Hoerig H, Kaufman HL. Immunotherapy for melanoma. Clin Dermatol 2004;22:251–65.

Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol 2003;4:748–52.

reported with DTIC alone, producing mean response rates of 25%, which are not significantly superior to DTIC alone. More activity has been reported in studies that combine cisplatin with IL-2 with or without interferon-α2b for metastatic melanoma. Objective response rates as high as 50% have been reported (10%–20% being complete responders), with median survival of about 11–12 months. Patients who were partial responders did not fair as well, having only a median response of 4–6 months without extended survival. Cisplatin appeared to be at least additive in this combination, and its activity appeared greatest when the chemotherapy was administered first. In this case, with the durability of complete response extending to 2 years for 10% of the population, biochemotherapy seemed to be potentially superior to either chemotherapy or immunotherapy alone.

In an attempt to make inpatient biochemotherapy regimens more practical and reduce the length of inpatient hospital stays, investigators have explored the administration of immunotherapy concurrent with chemotherapy. One regimen combining CVD with interferon-α2b and IL-2 over the course of 5 days, yielded objective response rates of 64%, and a median duration of response of 6.5 months; however, 9% of patients remained in remission for 50–61 months. Although adverse effects included substantial myelosuppression, a 54% incidence of febrile neutropenia, and 49% incidence of bacteremia, this course of therapy was deemed more manageable than other biochemotherapy regimens.

A slightly modified version of the CVD biochemotherapy method, the McDermott regimen, incorporates intensive supportive care into a treatment program. This treatment, which includes the use of antibiotic drug and granulocyte colony-stimulating factor prophylaxis, more aggressive antiemetic drug therapy with 5-HT_3 antagonists, and the restriction of long-term central venous access, resulted in enhanced tolerability without compromising therapeutic activity. Toxicities associated with this biochemotherapy resulting in dose reductions included nausea and vomiting and myelosuppression while hypotension and kidney dysfunction were relatively uncommon. The objective response rate was 48%, with a median duration of response of 7 months (ranging from 2 to 28 months).

A further modification to the McDermott regimen, in an attempt to enhance activity, added tamoxifen, granulocyte colony-stimulating factor, and IL-2 in a "decrescendo fashion." One of the highest complete remissions rates, 23% in patients with advanced melanoma, was the most notable outcome. However, all the complete responses were restricted to patients who had not been previously treated with chemotherapy. The overall response rate was 57%, and 32% of patients were still alive after 3 years of follow-up. Although the addition of tamoxifen seemed to benefit this treatment protocol, a subsequent study that included a high-dose tamoxifen arm found that addition of tamoxifen did not alter the outcome or improve efficacy.

All biochemotherapy regimens carry the risk of substantial toxicity, and the requirement for inpatient monitoring and rapid response to regimen-related toxicity is important to assure patient safety. Pharmacists should be aware of the multitude of supportive care issues surrounding the use of biochemotherapy in patients with melanoma. The application of these treatment strategies requires that the health care team be appropriately trained to deliver supportive care. By attending to and ensuring proper emesis control, pain management, neutropenia precautions, injection site monitoring, electrolyte status, hydration needs, kidney and hepatic toxicity monitoring, attending pharmacists help ensure a positive outcome in the management of patients receiving biochemotherapy. The substantial expense and patient time commitment makes the widespread use of biochemotherapy difficult. Furthermore, to date, Phase III studies have not confirmed the superior response reported in multiple Phase II trials.

One clinical trial comparing CVD with sequentially administered CVD with IL-2 or interferon-α2b reported both a doubling of the response rate (48% vs. 25%) and a prolongation in median survival time (11.9 vs. 9.2 months). The higher toxicity rates and 19-day inpatient hospitalization required for evaluation and treatment make this regimen an impractical treatment option in most settings. For example, 90% of patients in this trial required pressor support for hypotensive effects, and another 25% of patients had cardiopulmonary or neurological toxicity. Equally discouraging was the lack of difference in time to progression between the group that received biological therapy and the group that received chemotherapy alone. Additional European Phase III trials of similar biochemotherapy regimens have failed to confirm any added benefit of the combination of immunotherapy and chemotherapy and only reported more intense toxicities. A Phase III intergroup protocol designed to compare a modified concurrent biochemotherapy regimen involving CVD with interferon-α2b and IL-2 versus CVD alone is ongoing. It was hoped that the large estimated accrual of patients with advanced melanoma in this study would elucidate the true value of biochemotherapy relative to chemotherapy. Preliminary results released in abstract form have not confirmed the benefit of adding biological drugs to CVD, but have reaffirmed the enhanced toxicity associated with these regimens.

The future of biochemotherapy investigations involves the creation of treatment protocols that can enable a shorter duration of hospital stay while minimizing unacceptable toxicities. Several outpatient protocols of biochemotherapy using cytotoxic drugs followed by IL-2 subcutaneously with or without interferon-α2b are under way. Although these treatments are largely well-tolerated, a study comparing two outpatient regimens of cisplatin, DTIC, interferon-α2b, and IL-2 (given either subcutaneously or via intravenous bolus) showed that tumor responses were significantly lower in patients receiving the subcutaneous IL-2 (17% vs. 37%), indicating superiority for intravenously administered IL-2. The replacement of temozolomide for DTIC is being studied, not only to create a more convenient outpatient dosing regimen, but also to combat central nervous system relapses often experienced by patients with metastatic melanoma. One study reported a 47% overall response rate, but the median response duration was dishearteningly short, and the adverse effect profile was not different than that observed for DTIC. At this point, there is no justification for

substituting temozolomide for DTIC. Additional ongoing investigations are examining the role of maintenance IL-2 for those patients who respond.

Vaccines. As demonstrated above, melanoma is a relatively chemoresistant tumor, and the toxicities associated with biochemotherapy, along with the modest improvement in long-term survival, suggest that new therapeutic avenues for treating melanoma must be explored. Melanoma has long been recognized as the most immunogenic solid tumor type. Patients with melanoma have circulating cytotoxic T-lymphocytes and antitumor antibodies that are lethal to melanoma cells in vitro. These data and the known immune response resulting occasionally in spontaneous remission of primary melanoma lesions suggest that immunological approaches may hold the most promise as future therapeutic strategies for the cure of melanoma.

Vaccines that have been designed and studied in the clinic to date are based on a limited understanding of the type and role of each of the melanoma cell surface antigens. The cell surface antigens can be basically characterized as two specific types: the tumor-associated antigens and the melanoma-associated antigens.

Tumor-associated antigens are not specific to melanoma cells and include the latent expression of embryological antigens, antigens associated with previous viral exposure, and proteins from proto-oncogene expression. They can be present on a diverse number of solid tumor types and include MAGE-1, MAGE-3, GM2, GD2, GM3, and fetal antigens.

Melanoma-associated antigen, typically proteins or glycoproteins, include tyrosinase, the glycoproteins gp100 and gp75, MART-1, and high-molecular weight melanoma antigen. These antigens are found primarily on melanomas (occasionally on normal melanocytes) and are typically pathogenic for malignant melanoma.

Given the specificity of the melanoma-associated antigen, it may appear that development of a vaccine would be straightforward; however, the mutagenic nature of melanoma means that primary and metastatic melanomas may be quite different in expression of their surface antigen profile. In addition, most antigens are weak immunostimulants in their native state, which means that interaction with the patient's host immune defenses is minimal.

Although mutagenic antigens, such as the high-molecular weight protein, are uniquely present on the surface of individual tumors, these sorts of antigens make vaccine development in a large population of patients difficult. Rather, targeting antigens that are specific to both melanoma tumor cells and normal melanocytes have offered a more realistic approach to vaccine research and development. The categories of antigens as potential vaccine targets on melanoma cells include gangliosides, peptide antigens, and cell lysates.

The gangliosides are acidic glycolipids that are anchored into the plasma membrane of melanocytic cells, exposing the immunogenic sugars. GM2, GD2, and GD3 have been quite immunogenic in human trials. The first vaccine to show promise against a conjugate of the GM2 antigen with keyhole limpet hemocyanin and the adjuvant QS21 is GMK. This formulation produced immunoglobulin G antibodies to GM2 in nearly 100% of vaccinated patients and showed an improvement in relapse-free survival in patients who produced antibodies compared to Bacillus Calmette-Guérin. The subsequent study that compared GMK with interferon-α2b coincided with the FDA-approved labeling of interferon-α2b for adjuvant therapy of high-risk Stage IIB/III melanoma. The trial was terminated early due to the short-term effects of interferon-α2b, but vaccine supporters hope that additional follow-up of the study may provide indications of later effects that may result from an induced response from the vaccine.

Succeeding studies have shown that combining GMK with interferon-α2b does not decrease titers of anti-GM2 antibodies and that the two may be given together without diminishing the immunogenicity of the vaccine.

Another vaccine in clinical investigation targeted the GD2 antigen with a conjugated formulation that again used keyhole limpet hemocyanin and with QS21 as an adjuvant. The GD3 ganglioside antigen was also studied and produced antibody production, but a less than ideal immunogenicity rendered this vaccine further behind in investigations.

The use of mutated peptide antigens such as melanoma-associated antigen, melan A, tyrosinase, and glycoprotein-100 do not seem to stimulate a large enough immune response from the host when used alone in advanced disease. Rather, the use of multiple protein vaccines is hoped to elicit a more profound antibody production, as was reported with one study of a multi-epitope vaccine with or without granulocyte macrophage colony-stimulating factor and interferon-α2b. In several trials, this approach resulted in a longer progression-free survival compared with the use of a melanosomal differentiation antigen, tyrosinase, alone.

Cancer-testis antigens being investigated include BAGE, GAGE, and NY-ESO-1; results appear encouraging. There is hope that as the spectrum of available peptides expands with every recognition of a melanoma antigen by T cells, the continuum of all epitopes discovered will cover most types of melanoma.

Vaccines that are derived from whole cells or cell extracts have the interesting ability to generate immune responses against numerous antigens present in melanoma cells, including gangliosides and some of the aforementioned peptides. Melacine is a melanoma vaccine developed from the cell lysates of two human melanoma cell lines, which was studied in an adjuvant setting in patients with intermediate thickness tumors (1.5–4 mm). Although early results did not show an increase in relapse-free or overall survival, studies with longer term follow-up are in progress.

The FDA has designated one commercial vaccine, vitespen or formerly heat shock protein peptide-complex (glycoprotein)-96 (HSPPC 96) (Oncophage; Antigenics Inc.), for fast-track and orphan drug development for treating metastatic melanoma and renal cell carcinoma. This personalized vaccine is based on proprietary heat shock protein technology that is designed to capture the particular antigens that are specific to each individual's cancer. Heat shock proteins aid in the folding and disposal of proteins intracellularly, and when expelled from a cancerous cell, or in this case given as a drug product, are able to present

cancerous antigens to stimulate the host's immune system to create tumor specific antibodies.

The novel manufacturing process of vitespen incorporates heat shock technology to isolate HSPPC and its associated peptides from an individual patient's tumor that has been surgically removed and sent to the proprietor's manufacturing facility. On successful preparation, vitespen is returned to the hospital pharmacy to be given to the patient within 4–8 weeks. Several Phase II trials have indicated disease stabilization in a majority of patients with recurrent disease following surgery and a few complete responders per study. Vitespen has been given with granulocyte macrophage colony-stimulating factor and interferon-α2b as adjuvants to help stimulate the patient's immune response and antibody production. Phase III studies and analysis of clinical trial data are ongoing.

Future Directions. Considering the strong etiologic relationship observed between the origins of malignant melanoma and the altered function of the host immune system, it is natural that the recent focus in therapeutic melanoma research has been on vaccine-based immunotherapies, as mentioned above.

Other immune-based treatment modalities include a number of gene therapy-based vaccines that use viral or plasmid DNA delivery systems. Dendritic cells are being used as adjuvants to potentiate immune responses and cytotoxic T lymphocyte-associated antigen 4 inhibition, in the hopes of eventually enhancing T-cell-dependent immunity against melanoma.

A humanized anti-CTLA-4 monoclonal antibody, MDX-010, is currently being evaluated in Phase II studies for its role in increasing the response to vaccine therapies, such as gp100 peptide vaccine. Reported response rates were as high as 21% in patients with advanced melanoma, but toxicities were significant, including grade III–IV, dose-dependent, autoimmune-mediated manifestations reported in 43% of patients. Pharmacists practicing in these clinical settings should be prepared to treat autoimmune-type reactions and to combat such reactions appropriately with steroids or supportive care.

As with other cancers, defining new molecular targets for melanoma has shifted research efforts from broad-spectrum immunologically based targets to more focused molecular strategies. New insight into the molecular events that protect malignant cells from responding to cell death signaling cascades have led to greater understanding of how tumors, such as melanoma, become resistant to the induction of apoptosis. The methylation-mediated, downregulation of the APAF-1 gene; upregulation of the bcl-2 gene; and activation of mutations of the homologue B1 Raf (B-Raf) gene are resistant mechanisms being targeted as potential areas for new treatment approaches. Research into these pathways has produced targeted small molecules and antisense therapies that are currently being evaluated in clinical trials.

Although the bcl-2 oligonucleotide, oblimersen, was not active in single-agent studies in patients with metastatic melanoma, this novel antisense compound is currently under evaluation in several clinical trials in combination with traditional cytotoxic drugs, including DTIC.

Sorafenib (BAY 43-9006), an investigational serine-threonine kinase inhibitor, is now being studied for its ability to inhibit several different kinase targets, particularly the Raf pathway that is found to be dysregulated in several malignancies, especially melanoma. The B-Raf mutations are the most common oncogene mutations in melanoma, suggesting that they may be strongly correlated to the dysregulation of melanocyte growth and differentiation. However, these same B-Raf mutations are also present in 60%–80% of nonmalignant melanocytic nevi, indicating that perhaps the *ras*/Raf scaffold from which malignancy is thought to develop is more complex than initially imagined.

It is clear that for tumor types with intrinsic chemotherapy-resistance, such as pancreatic cancer and melanoma, traditional cytotoxic therapies hold little promise. Therefore, the development of therapies that target unique pathways, and in the case of melanoma both immunologic and molecular, will be the key to developing more successful therapies for treating these malignancies.

Special Populations

Patients with Solid Organ Transplant

Immunosuppressive drugs have an established association with melanoma and other cutaneous malignancies, and both degree and chronicity of immunosuppression are important factors. The transplant patient's increased risk for malignancy, melanoma, or other tumor types is believed due to the overall level of immunosuppression rather than the contribution of one particular medication. Because of this, therapies that incorporate three-immunosuppressive drugs versus double-drug regimens also confer a greater risk for melanoma. Much of the clinical data comparing immunosuppressive drug regimens are retrospective and only compare cyclosporine to azathioprine; to date, studies show no difference in the occurrence of melanoma between these therapies. Data on melanoma incidence with newer drugs, such as tacrolimus, mycophenolate mofetil, and rapamycin, are too limited to make conclusions.

In vivo and in vitro preclinical studies, in addition to clinical data from patient outcomes, have assessed the malignant potential of different immunosuppressive drugs.

The history of immunosuppressive drugs for patients with solid organ transplant began with the use of azathioprine in 1962, which has been found to promote carcinogenesis. Azathioprine is non-enzymatically cleaved to 6-mercaptopurine, which is then metabolized to the active 6-thioguanine nucleotides, which are then incorporated into DNA as a sham thio-guanosine nucleotide. Patients with higher circulating 6-thioguanine nucleotide levels have been at increased risk for developing cutaneous melanoma.

Cyclosporine has also been implicated to have malignant potential in preclinical studies. The induction of potential tumor growth is hypothesized to be a result of enhanced expression of transforming growth factor-β. Increasing expression of transforming growth factor-β has been

Pavlick AC, Adams S, Fink MA, Bailes A. Novel therapeutic agents under investigation for malignant melanoma. Expert Opin Investig Drugs 2003;12:1545–58. Review.

associated with an increased ability of tumor cells to mobilize and propagate. Furthermore, tumor-promoting effects of the calcineurin inhibitors cyclosporine and tacrolimus have been described in Epstein-Barr virus-infected cells, such as those noted in post-transplant lymphoproliferative disorders. Tacrolimus has enhanced expression of transforming growth factor-β messenger RNA and protein in a dose-dependent manner.

Compared with the above described drugs, newer immunosuppressive drugs may actually minimize the likelihood of cutaneous malignancies in patients with solid organ transplant. Sirolimus (rapamycin) may protect against cutaneous tumor development through anti-angiogenic mechanisms. One mechanism for this activity may be a decrease in production of vascular endothelial growth factor, leading to decreased angiogenesis and tumor growth inhibition as observed in in vivo models. Should this prove true, sirolimus should be used adjunctively with other immunosuppressive drugs in patients with solid organ transplant, thereby reducing the likelihood that these patients will develop cutaneous cancers.

Although a consensus opinion on the individual effects of each immunosuppressive drug has not been reached, the relationship between the use of these drugs and their role in the development of cutaneous skin cancers is recognized. Clinical trials of calcineurin inhibitors suggest that patients who have undergone an organ transplant and are receiving tacrolimus have a lower risk of developing cutaneous malignancies than those on cyclosporine. The older anti-metabolite, azathioprine, though largely phased out of immunosuppressive regimens in patients with transplants, is still used and considered to increase the risk for malignancy. Research focused on the use of sirolimus in patients with transplants demonstrates that it reduces the risk of malignancy in this population. Little data are available on mycophenolate mofetil, and further research is needed to illuminate its role in potential tumor development, particularly melanoma, in patients with transplants.

Topical immunosuppressive agents used to relieve the symptoms of mild to moderate atopic dermatitis have also come under scrutiny recently based on case reports of the use of tacrolimus and pimecrolimus creams and the possible association with malignancies and skin cancer. Pharmacists are now instructed to provide mandatory medication guides to patients. Tacrolimus and pimecrolimus creams are approved for short-term or intermittent treatment of atopic dermatitis in patients unresponsive to or intolerant of other treatments, and they should be considered a last resort. Tacrolimus and pimecrolimus creams should be used only for short time periods, not continuously. The long-term safety of these products is unknown. Children and adults with a weakened or compromised immune system should not use either product.

Patients Infected with HIV

Patients infected with HIV who have melanoma should continue treatment regimens with highly active anti-retroviral therapy because the regimens are highly effective against the HIV. No studies report using interferon-α2b in patients positive for HIV, but there are no contraindications to its use or the use of any other biotherapy therapy for adjuvant treatment. Individual patient characteristics should be taken into consideration whenever choosing the appropriate melanoma treatment regimen in this patient population. Interleukin-2 is also not contraindicated, and has recently been reconsidered as a treatment modality for HIV disease. Vaccine therapy does not appear to be a reasonable alternative for this population because their ability to mount an active immune response to a vaccine is blunted. To date, all vaccine trials have excluded patients with HIV infection.

Early Screening and Prevention

The most manageable melanoma is the one that does not exist; therefore, the importance of a public informed on the harmful effects of UV radiation and sunlight can never be overemphasized, especially for children and adolescents. Sunscreens are a good start, but may not be sufficient to thwart the potentially carcinogenic effects of UVA radiation. Therefore, excessive exposure to solar radiation and tanning devices should be discouraged. As previously mentioned, high-risk patients need to have their body surface examined by a professional at least annually, and they must incorporate use of sun exposure-deterring precautions such as protective clothing, use of broad-spectrum sun protection factor (at least 15) sunscreen, and avoidance of midday sun into their daily lifestyle. Last, self-examinations should be recommended for the entire population with an emphasis on changes in existing moles or development of new lesions.

The arms and shoulders can be excellent areas for patient self-surveillance; such surveillance identifies persons who could further benefit from a physician's examination. The ABCD mnemonic for evaluation can be promoted to identify suspicious moles based on asymmetry, border irregularity, color variegation, and diameter size. Because mortality for advanced disease has not been significantly reduced, all patients, but especially those who are at greater risk can benefit from the recommendations of the American Academy of Dermatology for monthly self-examinations and frequent clinical examination by a professional. Otherwise, for average-risk individuals, self-inspection with self-referral is adequate surveillance.

Chemoprevention

Chemoprevention is defined as the use of natural or synthetic drugs to reverse, suppress, or prevent premalignant lesions from progressing to invasive cancer. Candidate patients for chemoprevention include those with a familial risk of melanoma or those who have undergone successful primary cancer treatment, but are at an increased

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Wilkins K, Dolev JC, Turner R, et al. Approach to the treatment of cutaneous malignancy in HIV-infected patients. Derm Therapy 2005;18:77–86.

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risk of a second cancer. The relevance of UV-mediated carcinogenesis on the development of melanoma makes skin protection an obvious target. For melanoma, four postulated targets for chemoprevention are being actively investigated: 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, retinoids, cyclooxygenase-2 inhibitors, and imiquimod.

The use of 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors in melanoma chemoprevention studies is supported by clinical and preclinical data that elucidated a variety of mechanisms for their antiproliferative effects. It appears that 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors may have a role in interfering with deleterious cell-signaling cascades, particularly the *ras* pathway, thereby preventing cancer progression. In light of the growing data supporting the role of cyclooxygenase-2 inhibitors and retinoids as chemopreventive drugs in other cancers, these drug classes are also beginning to be investigated for treatment of melanoma. Imiquimod is a topical immune response modifier labeled for treating perianal warts and for treating actinic keratoses, precancerous skin lesions. Imiquimod works through Toll-like receptors, particularly TLR-7, to stimulate the immune system. Further investigation is needed before any of these drugs can be recommended for chemoprevention.

Patient Education

During systemic treatment with cytotoxic chemotherapy or highly active biological drugs, all patients with melanoma will experience a range of adverse effects from mild to profoundly unacceptable. During counseling with patients, pharmacists should emphasize that their regimen can be important in assuring quality outcomes. Improving patient awareness on the potential adverse effects of therapy before treatment enables patients to better communicate their treatment experience with the health care team.

Enhancing patient communication with the oncologist, pharmacist, and nursing staff ensures that supportive care measures are properly implemented. Patients should contact any or all members of the health care team if they notice changes in appetite, nausea and vomiting, or headache. Educating patients about drugs that can combat nausea and vomiting, pain, diarrhea, anxiety or any other symptoms before initiating the treatment can help ease tensions for patients and their families.

Quality Improvement

The treatment of melanoma with chemotherapy, biological drugs, or both is not completely standardized due to the variability in melanoma staging and each patient's individual performance status. As summarized above, the prognosis of melanoma is often reflected by the severity and invasiveness of tumor proliferation. Surgical excision of early-diagnosed melanocytic lesions is the most effective treatment approach. For melanoma with nodal involvement, sentinel lymph node biopsies provide accurate staging techniques, but the therapeutic efficacy of complete nodal dissection is still unproven. In regard to adjuvant therapy for patients after having surgery, no treatment has proven superior to any other, and metastatic disease remains a medically difficult challenge for treatment.

Response and Survival

With a staggering increase in the diagnosis of malignant melanoma over the past 3 decades, coupled with the lack of improved therapies for advanced disease, the need for more effective prevention and treatment strategies cannot be overemphasized. Improvement in both the durability of response and long-term survival is urgently needed, especially for advanced disease. Although many of the treatment approaches described above have increased initial response rates, they have little impact on disease cure. The use of chemotherapy, biotherapy, and biochemotherapy has added at most a few months in survival in advanced or metastatic malignancy. The future of melanoma disease control lies both in educating the population on the direct relationship between UV exposure and disease and in furthering the understanding of the molecular and immunological mechanisms behind melanoma growth, development, and metastasis. New therapeutic approaches need to be designed for this devastating disease.

Efficacy

In the case of adjuvant therapies, the role of interferon-α2b is often considered a first-line treatment, but the situation is less clear as disease progresses. Although response rates of combination chemotherapy or biochemotherapy regimens can range up to 55% for advanced disease, the ineffectiveness of these combination regimens to elicit a clear improvement in survival over single-agent DTIC for metastatic melanoma does not allow any support for standardized treatments. Benchmark studies are nonexistent when it comes to identifying the one best standard of care by which all metastatic therapy should be guided. The relatively consistent 10%–20% response rates reported with single-agent DTIC for metastatic melanoma suggest that this is probably the best option for most patients, particularly patients with poorer performance status or those in need of a regimen with a manageable toxicity profile. Patients with no comorbidities who boast a strong performance status may be eligible for combination treatment options in the hopes of extending durable response, which has been observed with some regimens such as CVD. Clinical trials are always viable options for patients who do not respond to standard therapy. As previously described, patient characteristics, disease stage, and past treatment history largely determine the treatment and outcome.

Educating patients about the importance of skin self-examination and of seeking medical attention for suspicious nevi can yield the greatest efficacy in detecting a potentially malignant lesion. With the aid of a health professional, the detection of suspicious malignant lesions can lead to complete excision of the nevi, preventing a potentially dangerous invasive growth pattern that may result from negligence.

Efficiency

The pharmacist's role in the health system has become increasingly vital, particularly when it comes to the ability of pharmacists to create cost-containing strategies in using quality pharmaceutical care. Prevention is, by far, the most efficient method for curtailing the tremendous costs

associated with melanoma treatment. The survival benefits of early-stage melanoma treatments are clearly documented in the literature. Considering that the annual direct cost for treating newly diagnosed melanoma in one estimate from 1997 was $563 million, with Stage III and IV disease contributing to 34% and 55% of the total cost, respectively, the importance of aggressive primary prevention should greatly reduce the economic burden of melanoma care. Although patients with Stage III and IV melanoma represent less than 20% of the total treatment population, the cost of their care composes 90% of the total annual direct cost associated with the treatment of this disease. Medicare projections of these costs balloon to $5 billion by 2010.

Therapeutic monitoring of indices such as serum creatinine for kidney function and liver enzymes for assessment of hepatic function are often important criteria for proceeding with the administration of expensive chemotherapy and biological medications, as well as guarding from untoward complications that can result in increased cost of therapy and increased duration of hospitalization. From the perspective of the hospital pharmacist, whether a decentralized clinician or staff practitioner is responsible for drug validation and distribution, suspending drug delivery that does not meet criteria outlined in chemotherapy/biochemotherapy protocols can be life-saving and cost-saving. Pharmacists also may affect the cost of therapy by thorough and objective evaluation of costly new drugs. Appropriate monitoring and supportive care for therapy-induced toxicities can lead to a decreased need for additional therapies and a decreased length of hospital stay. All of these pharmacist-led interventions can guide cost savings for the patient and the treating health care center.

Effectiveness

A delay in melanoma diagnosis is a common oversight that can lead to invasive, advanced disease requiring extensive therapy with a decreased chance for survival. The major component of delay is often due to patients. A general lack of concern is cited often as the most notable reason patients do not seek early medical attention. Various studies have reported that more than 50% of patients delay the reporting of a suspicious lesion to a physician by an average of 2 months. A highly visible tumor and higher educational or socioeconomic status of patients appear to improve earlier diagnosis of melanoma. In almost 25% of patients who first had a suspicious nevi or lesion observed by a physician, the mean time to actual excision of the lesion was 2.5 months. This delay can be attributed to misdiagnosis of an initial lesion or a delay in scheduling a surgical referral. Clearly, more timely reporting and referral by both patients and physicians are needed to increase the likelihood of cure for this disease.

Currently used treatment strategies, excluding surgery, offer little in the way of effective, disease-curing options. There is a need for newer drugs that use the host immune system to mount an effective tumoricidal attack. Much current research is focused around the development of patient-specific vaccines and their potential integration into therapies using drugs to target specific molecular defects in melanoma. Small molecules capable of interfering with molecular pathways involved in the regulation of cell death, invasion, vascular growth, and immunological function are nearing clinical investigation. Many drugs show promise in preclinical models of melanoma and may be available in the next few years.

Pharmacoeconomics

Cost-of-illness studies of the care of patients with melanoma are few. The cost, quality of life aspects, and cost-effectiveness of the use of adjuvant interferon-α2b in patients with melanoma are most studied. One study conducted in 1997 of the treatment history of a cohort of patients with newly diagnosed melanoma yielded the estimated annual costs for treating patients at each stage of diagnoses. The annual per patient treatment cost (in 1997 dollars) the first year after diagnosis was $1,310 (US dollars) for stage I, $3,299 for stage II, $41,670 for stage III, and $42,410 for stage IV. Of the patients with stage IV disease, 90% were assumed to receive chemotherapy and 30% some external radiation. For patients with stage IV disease, 85% of the annual costs were associated with patients receiving chemotherapy and terminal care. In patients with stage III disease, 80% of the total cost was attributable to interferon-α2b treatment; however, only 30% of patients receive this therapy. The technological developments of sentinel node mapping and interferon-α2b therapy have had the greatest impact in increasing the overall cost of therapy for patients with stage II and III disease. Another study pooled cost data for all professional, clinical, laboratory, and pharmacy services along with patient visits, and determined an average point estimate per patient across all disease stages to be $59,440 in 1997–98. This same value was then compared with treatment, excluding all clinical research costs related to the use of immunomodulators, such as interferon-α2b and IL-2, in the adjuvant setting and the value was then $28,770, irrespective of patient stage. Immunotherapy costs were the highest, accounting for 47% of the total cost, while surgery was second with 13.5%, and treatment for progression without surgery (8.4%) and chemotherapy (8.2%) followed.

Most pharmacoeconomic models seem to confer a long-term gain of 2–3 years in the best clinical case with high-dose interferon-α2b. The incremental cost-effectiveness ratio in a best-case scenario such as this yields a cost per life-year gained of less than $20,000 for treatment, which is generally considered acceptable when comparing new therapies in oncology. But the high level of toxicity associated with high-dose interferon-α2b may carry with it a negative impact on cost-effectiveness, as it decreases the quality of life of patients in the first year of treatment. This issue should be taken into consideration on an individual basis for each patient who may be potentially treated with interferon-α2b.

The cost of treating melanoma is highly variable and differs greatly by settings. Until a standard treatment approach is adopted, pharmacists may be the first to recognize the impact that expensive immunomodulating therapies will have on the overall cost for each patient with melanoma.

Abbreviations

The Pharmacists' Role

Pharmacists play a fundamental role in managing patients with melanoma. Whether the treatment requires inpatient hospitalization over several days or treatment at an outpatient infusion clinic or clinical trial research center, pharmacists are responsible for recommending appropriate dosing for chemotherapy schedules, managing treatment-related toxicities, and continued improvement of pharmaceutical care.

Pharmacists must apply their knowledge of the toxicity profiles of chemotherapy regimens and biological drugs, and provide important supportive care prophylaxis to ensure positive outcomes with minimal toxicity and patient suffering. With advances in treatment complexity and supportive care needs, the practice responsibilities of pharmacists providing care to cancer patients has been evolving. Prospective control of nausea and vomiting, and timely pain management techniques are key factors to promoting a better quality of life for patients with melanoma. The detrimental effect that myelosuppression can have on survival is not trivial, and appropriate use of colony-stimulating factors and erythropoietin is essential for the use of chemotherapeutic agents and biochemotherapy in this patient population. The timely and appropriate initiation of antibiotic drugs in the patients experiencing febrile neutropenia during treatment for melanoma is imperative. The use of each of these therapeutic and supportive care modalities in special populations—such as the elderly; patients with multiple comorbidities or poor performance status; and those receiving biological therapies, such as interferon-α2b or IL-2, or intensely toxic multiagent regimens—must be understood. Providing toxicity monitoring is a vital function of pharmacists treating patients with melanoma who are receiving systemic cytotoxic or biological therapy, including investigational drugs.

In addition, pharmacists who work closely with oncologists need to understand the pathophysiology of melanoma in order to determine the most appropriate therapeutic intervention for this disease by stage.

Conclusion

The most effective strategy for reducing the impact of melanoma on the population is prevention. Pharmacists can greatly affect patient education and increased public awareness of this health issue. As the most accessible providers of health information, it is their duty to educate people on the importance of developing a solar protection plan. Selection of an appropriate sunscreen, along with its correct application and the use of protective clothing, should always be stressed as one part of a more complete plan.

When systemic treatment of this disease is necessary, pharmacists should provide the health care team with the information necessary to make a decision on the appropriate course of chemotherapy, biotherapy, or biochemotherapy. In addition, pharmacists should be capable of developing a monitoring strategy for the attendant complications that may arise using these therapeutic drugs, which possess serious and diverse adverse effects.

Annotated Bibliography

1. Danson S, Lorigan P. Improving outcomes in advanced malignant melanoma: update on systemic therapy. Drugs 2005;65(6):733–43.

   The research summarized in this review article brings the reader up-to-date on advances in investigations of newer cytotoxic chemotherapies, such as temozolomide and fotemustine. Use of drug resistance modifiers that aid in enhancing the activity of cytotoxic therapies in drug resistant tumor cells is addressed. Studies of targeted therapies such as the pro-apoptotic B-cell lymphoma-derived protein (bcl-2) antisense inhibitor, oblimersen, and various anti-angiogenesis drugs, including lenalidomide, semaxanib, and bevacizumab, are also summarized. In addition to cytotoxic compounds and small molecule inhibitors, this review article provides an excellent summary of the vaccine trials completed to date, as well as new advances in the use of immunomodulatory drugs. The treatment strategies discussed will help pharmacists stay abreast of current developments in melanoma research.

2. Atkins MB, Lee S, Flaherty E, et al. A prospective randomized phase III trial of concurrent biochemotherapy (BCT) with cisplatin, vinblastine, dacarbazine (CVD), IL-2 and interferon alpha-2b (IFN) versus CVD alone in patients with metastatic melanoma (E3695): an ECOG-coordinated intergroup trial. Proc Am Soc Clin Oncol 2003;22:708. Abstract. #2847.

   The objectives of this study were to answer questions concerning the superiority of biochemotherapy over chemotherapy, and to assess the survival benefit of adding interleukin (IL)-2 and interferon-α2b to cytotoxic therapy. Patients were randomly assigned to receive cisplatin, vinblastine, and dacarbazine (CVD) (cisplatin 20 mg/m^2/day; vinblastine 1.2 mg/m^2/day, both on days 1–4; and dacarbazine 800 mg/m^2 on day 1 only) either alone or concurrent with IL-2 (9 million units/m^2/day by continuous infusion on days 1–4 and interferon-α2b (5 million units/m^2/day subcutaneously on days 1–5, 8, 10, and 12). Treatment cycles were repeated every 21 days for a maximum of four cycles. This is a powerful study due to the overall number of patients enrolled (416), which allowed for statistical assessment of the survival advantage. The randomization used in this study was sufficient to allow for a sound assessment of each therapy, and no patient had received IL-2 or chemotherapy before. This study did not confirm any survival benefit in patients receiving biochemotherapy despite the group's slightly higher initial response rates. Additional follow-up will be required to assess the durability of response in long-term survivors to confirm an advantage of one treatment approach over another. However, the increased grade IV toxicity observed in patients on biochemotherapy (64% in biochemotherapy group vs. 37% in the chemotherapy group) suggests against the current use of this approach as standard therapy for patients with metastatic melanoma. Again, this study was, to date, one of the best Phase III trial study designs in assessing the effects of biochemotherapy. The full article has not yet been published.

3. Eggermont AM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years? Euro J Cancer 2004;40:1825–36.

   In the face of increasing numbers of clinical trials evaluating various chemotherapy and combination biochemotherapy regimens, this review article is an excellent summary of the role of dacarbazine in the treatment of

melanoma. With no other single-agent chemotherapy available that provides response rates or benefit comparable to dacarbazine, this historical review and update provides an excellent summary and explanation why dacarbazine is still considered the standard therapy to which complex chemotherapies and biochemotherapy should be compared.

4. Crott R. Cost-effectiveness and cost utility of adjuvant interferon-alpha in cutaneous melanoma: a review. Pharmacoeconomics 2004;22(9):569–80.

There are few pharmacoeconomic analyses comparing various treatment modalities for melanoma. Previous studies have established that patients with stage III and IV disease have the greatest cost of treatment, primarily due to use of adjuvant immunomodulators such as interferon-α2b. The author stresses that although the results of many published analyses provide support for the more widespread use of adjuvant interferon-α2b in the treatment of melanoma, these recommendations were based on only two positive clinical trials out of a total of 10 studies. In addition, the impact on survival was lost in both of the trials showing benefit when follow-up extended beyond 8 years. Ensuring appropriate use of expensive biological drugs is a primary responsibility for most pharmacists. This article is extremely useful for any pharmacist who desires to accurately define, or redefine, the pharmacoeconomic use of interferon-α2b in his or her institution.

5. Demierre MF, Sondak VK. Cutaneous melanoma: pathogenesis and rationale for chemoprevention. Crit Rev Oncol Hematol 2005;53:225–39.

This article provides the reader insight into the role played by chemopreventative drugs in the prevention of malignancies, particularly melanoma. The lipid-lowering drugs, the 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, are reviewed as the most likely promising drugs. This article suggests that 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, which can target the *ras* cell-signaling pathway—a pathway that has been implicated in carcinogenesis—could potentially be used for chemoprevention of melanoma. The preclinical and clinical data used to support the use of retinoids, cyclooxygenase-2 inhibitors, and Toll-like receptor activators such as imiquimod are also summarized in this review. This insightful article presents a strong pharmacological rationale for the use of available drugs for the prevention of melanoma.