Early detection and treatment of skin cancer

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The most deadly but less common form of skin cancer, melanoma is now the most common cancer found in women between the ages 25 to 29 and is the second only to breast cancer in women of ages between 30 to 34. It is believed that increased sun exposure, along with a decreased ozone layer are major causes of the increased incidence of skin cancers. Skin cancer is a highly preventable disease and many are cured if diagnosed early in its development. Surgery continues to be the mainstay for patients with an early diagnosis. Other conventional therapies, such as radiotherapy and chemotherapy are progressing slowly and attention is being shifted towards combination therapy and other novel approaches. This article is aimed to update the knowledge of the reader about the types of skin cancers and to discuss the current treatment options available. [Turk J Cancer 2002;32(4):129-137]

Key words: Melanoma, radiotherapy, chemotherapy, immunotherapy, gene therapy, vaccine therapy

There are three major types of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. Basal cell carcinoma and squamous cell carcinoma are also known as nonmelanoma skin cancers.

A. Nonmelanoma skin cancers

Basal cell carcinoma arise in the epidermis and accounts for more than 75 percent of all skin cancers. Basal cell carcinomas are often found on the face or the back of hands but may occur in any part of body that has been exposed to the sun. They typically grow slowly and generally only spread locally but if they recur after surgical excision they may present a greater risk of metastasis (1-3).

Twenty percent of all cases of nonmelanoma skin cancers are squamous cell carcinoma (SCC) and it is also the most common tumor among the elderly. Squamous cell carcinomas often arise from the upper level of the epidermis that have been exposed to the sun (the hands, the head and neck, the ears, the face and the mouth). Squamous cell carcinomas can rapidly grow to centimeters in size over a period of months and are slightly more likely to spread to other parts of the body.

These type of cancer may arise from a precancerous lesion (Actinic
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keratosis) that appears as rough, red or brown scaly patches on the skin, usually in areas that have been exposed to the sun (2,4). SCC may also appear in the areas that have been subjected to ionizing irradiation or in other locations in patients that have undergone treatment with immunosuppressive drugs or have been exposed to organic trivalent arsenic compounds or tars.

B. Melanoma

Melanoma is the most serious form of skin cancer and it develops in the melanocytes, the cells in the epidermal layer of the skin that produce the pigment melanin. There are four major subtypes of melanoma that are distinctive in development and clinical features: a) Superficial spreading melanoma, b) Nodular melanomas, c) Lentigo maligna melanoma and d) Acral lentiginous melanoma.

Superficial spreading melanoma is the most common morphological type of cutaneous melanoma and accounts for about 70% of all melanoma. A dark brown or black lesion usually evolves slowly over 1 to 5 years from an existing nevus.

Nodular melanomas develop more rapidly and are typically dark blue-black and often uniform in color. They grow vertically from the beginning and often appear raised and symmetrical or dome shaped. Nodular melanomas can occur at any age and are most common on the trunk, head and neck (5).

Lentigo maligna melanomas are generally large (greater than 3 cm), flat, and tan colored lesions with shades of black and brown. Lentigo maligna melanoma typically appears on the face of the elderly.

Acral lentiginous melanoma is often located on the sole of the foot and appear as a large (greater than 3 cm) tan or brown stain with an irregular, convoluted border. This subtype of melanoma can also appear on the palms of hands and beneath the nailbeds (6-8).

Although melanomas are seen on the back and face of men and on the legs of women they may arise in digestive tract or other areas in the body where melanocytes are found (2). Other kinds of cancer that may affect the skin include cutaneous T-cell lymphoma, a cancer of the lymph system and Kaposi’s sarcoma (7,9).

Detection and Diagnosis

Due to the visible nature of the disease, early detection of skin cancer plays a vital role and regular head-to-toe examination is the key to diagnose skin cancer at its earliest stage, when its most easily cured. Basal cell carcinoma and squamous cell carcinoma are generally diagnosed in the same way. When an area of skin does not look normal (color, size etc.) the doctor may remove all or the part of the growth (biopsy) to determine if any cancer is present (2,6).

As mentioned previously, a variety of skin lesions are considered precursors to squamous cell carcinoma. Actinic keratosis (is also called solar keratoses) are ill-defined and irregular lesions ranging from 1 mm to several centimeters in size (very similar to less severe lesions of SCC) and it always appears on chronically sun-damaged body areas, such as the ears, face, arms and hands. The mnemonic “ABCDE” has been developed to describe or evaluate
suspicious lesions or moles and to help people recognize melanoma at an early stage (Table 1) (2,4).

<table>
<thead>
<tr>
<th>Checklist Item</th>
<th>Suggesting Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Asymmetry</td>
<td>Noncancerous, symmetric and circular in shape; usually growing in an irregular, asymmetric fashion</td>
</tr>
<tr>
<td>B. Border irregularity</td>
<td>Notched or indistinct borders that can signal ongoing growth</td>
</tr>
<tr>
<td>C. Color variation</td>
<td>Often appear tan, dark brown, or black. Occasionally flesh colored or surrounded by pink or red areas that arise from inflammation of blood vessels within the skin. Blue areas can appear due to the pigment in the deeper layer of the skin and even white areas can arise from dead cancerous tissue</td>
</tr>
<tr>
<td>D. Diameter</td>
<td>Greater than 6 mm</td>
</tr>
<tr>
<td>E. Evolution</td>
<td>Recent change</td>
</tr>
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</table>

Although melanomas may lack one or more of these features, one feature especially a combination of features should raise suspicion of malignancy. Early detection through self-examinations has shown up to a 63% reduction in melanoma mortality and counseling patients at risk for skin cancer should include at least monthly self-examinations.

**Treatment of Skin Cancers**

Treatment of skin cancer depends on the type and stage of the disease, the patient’s age and overall health. Standard treatment for skin cancer involves surgery, laser, chemo-, radiation or biological therapy. However, not all patients are cured with standard therapy and some standard treatments may have more side effects than are desired. For these reasons, clinical trials are designed to find better ways to treat cancer patients.

**A. Treatment of nonmelanoma skin cancers**

Low risk lesions of SCC or BCC are cured 95-99 percent of the time using simple surgical excision. Depending on the tumor location and size, the patient’s general health, treatment options may include curettage and electrodessication, radiation therapy or Moh’s surgery. Moh’s surgery is used to remove large tumors, tumors that are difficult to excise or cancers that have recurred. The purpose of Moh’s surgery is to remove all of the malignant tissue with as little healthy tissue as possible. The degree of scarring depends on the location and the size of the treated area.
Radiation therapy may be used for skin cancers that occur in areas hard to treat, such as the eyelid, tip of the nose or ear. However, radiation exposure is a risk factor for skin cancer many years after the treatment therefore it is not often used for young patients.

Cryosurgery, electrodessication and laser surgery are sometimes used to treat nonmelanoma skin cancers and other skin lesions (i.e. Actinic keratoses). 5-fluorouracil (5-FU), a pyrimidine antagonist that inhibits DNA synthesis, may be used for the chemical destruction of many superficial lesions present on the face and head. 5-FU (1,2 and 5 percent solutions or 1 and 5 percent creams) is usually applied twice daily for two to five weeks with areas of greater skin thickness requiring the higher concentration. The patient may experience significant discomfort related to the strong inflammatory response and adverse effects include true hypersensitivity, secondary bacterial and herpetic infection, and post inflammatory pigmentation changes. The role of topical tretinoin in the management of actinic keratoses remains to be shown and although tretinoin is capable of reversing photodamage, the effect is not permanent and requires maintenance therapy (2,5,10,11).

B. Treatment of melanoma

Surgical treatment is curative for most early stage melanomas and is the treatment of choice when the melanoma is confined to the skin and does not extend beyond regional lymph nodes. Despite an extensive effort in various treatment regimens, the prognosis of patients suffering from metastatic melanoma remains poor. The treatment options tested have ranged from monochemotherapy, polychemotherapy (including regimens requiring autologous bone marrow rescue), immuno-modulatory approaches and vaccination (12,13).

Surgery

Surgery is the primary treatment for all stages of melanoma and a biopsy is required to remove some or the entire lesion. Surgery may also be an appropriate option as palliative treatment once the patient’s comfort and quality of life is evaluated. Lymph node removal is indicated in cases where the melanoma is larger than 4 mm or if the lymph nodes are a site of metastasis (14). The most essential and important aspect of surgical management is the post-surgical follow-up of patients. After excision there still remains a risk of undetected metastatic disease, risk of developing a second primary cutaneous melanoma, and the risk of a second nonmelanoma primary malignancy. Scheduled screening and routine surgical follow up is required for anyone who has had a melanoma. The frequency and duration recommended is dependent upon the stage of melanoma (15).

Monochemotherapy

Dacarbazine (DTIC) is still the only agent approved by the FDA for the treatment of melanoma with a response rate of approximately 25%. DTIC is an alkylating agent that undergoes activation in the liver via oxidative metabolism to its active metabolite methyl-triazeno imidazole carboxiamide (MTIC). DTIC
may be given intravenously as a 1-day or 5-day regimen at 850 mg/m^2 or 250 mg/m^2, respectively. Dose-related photosensitivity do occur rarely but patients should be advised to stay out of the sun for several days following treatment. Blood counts and liver functions test should be obtained routinely during treatment (16,17).

Temozolomide is an imidazotertrazine prodrug that is currently being investigated in the treatment of metastatic melanoma. Temozolomide at physiological pH spontaneously converts into MTIC without the need for active hepatic metabolization. In contrast to DTIC, temozolomide efficiently crosses the blood-brain barrier where it converts to MTIC and gains it alkylating activity. This property has shown activity against tumors within the CNS, including those of melanoma metastases and is approved by the FDA for the treatment of glioma. Temozolomide is administered as an oral formulation with almost a complete absorption if taken in a fasting state (18,19).

The nitrosureas, i.e. carmustine, lomustine and fotemustine are cytotoxic agents that have shown activity against melanoma. As with the other therapeutic agents, response rates are low and are predominantly seen in the skin, subcutaneous tissue, lymph node and the lungs. The rationale of using nitrosureas were the possible added benefit in a malignancy that can metastasize to the brain. Although lyophilic nitrosureas have the ability to cross the blood-brain barrier, studies thus far have not shown an increase in response in melanoma in the CNS (15).

Combination therapy

The most widely used and extensively studied combination chemotherapy is that of the Dartmouth regimen consisting of DTIC, cisplatin, carmustine and tamoxifen. In the initial single-institution phase II trial, the Dartmouth regimen induced a major tumor response in 40-50% of stage IV melanoma patients. However, two recent trials have reported that the regimen of DTIC, cisplatin, BCNU and tamoxifen offer no discernible survival benefit over DTIC alone in treating stage IV melanoma (12,20,21).

Several large, randomized trials have failed to show a benefit for chemotherapy in patients at high risk of relapse following excision of the primary melanoma and/or nodal metastases and presently serves no role in the adjuvant setting (22).

Immunotherapy

Melanoma is known to be one of the most immunogeneic solid tumors and seems to interact with and respond to the immune system of the host. Melanoma is also one of the most resistant tumors to the conventional therapies of radiation and chemotherapy. Immunotherapy has the ability to play a significant role in the treatment of melanoma, specifically if surgery fails. Cytokines are one group of immune factors being studied for their effects on melanoma. Due to their high toxicity, interferons (IFNs) and interleukins (ILs) are primarily being studied to improve survival rates in combination with other agents or regimens. IFN-α has a direct action on tumor cells being cytostatic, promotes tumor cell differentiation and enhances the major histocompatibility complex h(MHC) and tumor-associated antigen expression. IFN-α has also
shown to enhance natural killer cell, macrophage and T-lymphocyte function as well as possessing angiogenic properties (22). Initial clinical trials with IFN-\(\alpha\) in metastatic cutaneous melanoma demonstrated that the response rates proved best in patients with minimal disease (23). IFN-\(\alpha\)2b was studied as an adjuvant therapy following surgery for deep primary or regionally metastatic melanoma. The toxicity was severe and approximately half of the patients required dosing delays or dose reductions but the results did suggest the benefit outweighed the toxic effects (24,25). IFN therapy side effects can be classified as constitutional symptoms, such as acute symptoms of fever, chills, myalgia, and the more chronic conditions such as fatigue, anorexia and depression and IFN therapy is also associated with hematologic and hepatic toxicity. Acetaminophen is used to prevent or minimize the acute dose-related symptoms and opiates are often required when patients experience severe chills or rigors (15,22).

Interleukin-2 is a glycoprotein produced by activated lymphocytes and its precise mechanism of action is unknown. IL-2 is thought to act through a variety of mechanisms including activation of cytotoxic T-cells and natural killer cells along with the production of other cytokines but has not been shown to have a direct anti-tumor effect on cancer cells in vitro. The toxicities of IL-2 are severe and include flu-like symptoms with dose-limiting side effects of hypotension, vascular leak syndrome, renal, gastrointestinal and hematological toxicities. Despite it’s high toxicity, IL-2 is the only other cytokine besides IFN-\(\alpha\)2b that is currently FDA approved in the treatment of metastatic melanoma (22).

Vaccines

Instead of protection from infectious disease, cancer vaccines are used therapeutically and can take several months to show a beneficial effect. The tumor reduction that occur with the use of the vaccine will be longer lasting than that of chemotherapy and hopefully possesses fewer side effects than that of the cytokines. Vaccines are being investigated alone and in combination with other immunotherapeutic agents and are now in the advanced stages of development. Vaccine immunotherapy uses melanoma-associated cells to serve as antigens in order to allow the body’s immune system to mount a beneficial response. Melanoma antigens are either tumor-associated antigens (TAAs) or melanoma-associated antigens (MAAs). TAAs are common to melanoma and tumor cells and MAAs are usually proteins or glycoproteins that are found in melanomas or in normal melanocytes (26). Most vaccines use two basic approaches, autologous and allogenic (or in combination). Autologous vaccines are made using the patient’s own tumor and have the main advantage of inducing an immune response against the patient’s own tumor antigens. One problem with this approach is that there is not a standard method to scientifically assess the outcome or success since each vaccine is unique to the individual patient. Allogenic vaccines rely on commonly shared antigens and are easier to manufacture than autologous vaccines. Allogenic vaccines have the advantage of producing a broad range of protective immune responses with potential disadvantages encompassing immune responses from other vaccine components that are not melanoma associated or the induction of antimelanoma-immune response to target antigens that are absent on the patient’s specific tumor (27).
A polyvalent melanoma vaccine (CancerVax) containing three viable irradiated allogenic melanoma cell lines chosen for their antigenicity have been extensively studied (28,29). Phase II studies of this vaccine in AJCC stage IV melanoma demonstrated a survival advantage for patients treated with vaccine when compared to historical controls treated with non-vaccine therapies (25% for 157 patients treated with vaccine, 6% for control group, \( P=0.0001 \)) (28,29). In general, the antitumor activity of a polyvalent vaccine is less susceptible to antigenic modulation by cancer cells, although immune responses to irrelevant antigens and induction of tolerance are a potential disadvantage of complex vaccines. Another allogenic vaccine is Melacine, which is a lysate vaccine prepared from two human melanoma cell lines administered with an adjuvant immunostimulant monophosphoryl lipid A (MPL) and purified mycobacterial cell-wall skeleton called DETOX. Trials to date have not been conclusive to suggest a role for this particular vaccine (27,30).

In summary, improved diagnosis and treatment of malignant melanoma have led to high survival rates but there is still incidence of poor prognosis. While surgical excision is an effective treatment for patients with early and localized disease, it is not considered a useful intervention for patients with advanced melanoma. Radiotherapy is employed as a prognostic indicator in detecting melanoma, yet malignant melanoma is relatively resistant to radiotherapy. Likewise, some chemotherapy approaches for melanoma achieve response rates of \( \sim 50\% \) but reported survival rate data clearly demonstrates the need for improved treatment approaches. Immunotherapy is already established as an available method in treating the advanced melanoma, however, its limitations and potential problems should always be under consideration. On the other hand, advances in vaccine development involve genetic engineering of tumor cells and the characterization of MAA have led encouraging clinical results in melanoma patients with stage IV disease. Most importantly a general understanding of the contributing factors associated with skin cancer, along with a working knowledge of current treatment options and the ability to recognize a suspected lesion will all be beneficial for proper counseling.

References

8. Balch CM, Houghton AN, Peters LJ. Cutaneous melanoma In: DeVita,


25. Kim TF. Don’t waste more time on interferon in melanoma. Skin Allergy News June 2000:34.