

2002

Conn's
Current
Therapy

acute erythema, PUVA lentigos, and skin cancer (including melanoma), the latter usually identified years later. Patients should be screened with an anti-nuclear antibody (phototoxicity is an issue here) and eye examination. Protective glasses must be worn for 24 hours after psoralen treatment to protect the eyes from the risk of cataracts or retinal damage.

A third possibility for treatment of alopecia areata is the category of drugs known as hair growth promoters, of which topical minoxidil is the prototype. Data suggest that 5% topical minoxidil can be an effective single agent in limited patchy alopecia areata or as an adjuvant to systemic corticosteroid or topical anthralin use in the treatment of more extensive alopecia areata.

TRICHOTILLOMANIA

Patients with trichotillomania are usually adolescents, primarily girls, who generally present with a history of inexplicable treatment-refractory hair loss. The hair loss is generally patchy, although it can be diffuse, and consists of a decrease in the density of hair as well as scattered short hairs generally 1 to 2 mm in length in the affected area. Examination of the remaining hairs, which generally must be removed by a forcible hair pluck versus hair pull, reveals anagen hairs with broken, tapered, or cut distal ends: the broken ends reflect the breakage associated with pulling anagen hairs, tapered tips reflect newly regrowing hairs, and the cut ends reflect the not uncommon habit of these children to cut, if not pull out, their hair.

Trichotillomania is not a diagnosis likely to be supported by history because usually the child is not prepared to be honest regarding the etiology and the distraught parents are generally clueless and actually defensive about the potential self-induced nature of this problem. Confirmatory evidence can be produced by a scalp biopsy in an affected area that will show an increase in catagen hairs, pigment casts in the isthmus or infundibular area of the follicle, and damaged or empty follicles. Treatment requires acceptance of the diagnosis by the child and parents, reassurance that this is not necessarily evidence of a life-long disabling psychiatric disorder, and referral for counseling.

TINEA CAPITIS

Tinea capitis is a common problem that can occur at any age but is most common in poor African-American children. There are three clinical presentations: (1) a seborrhea-like scale on the scalp with thinning of the hair in the involved areas, (2) areas of noninflammatory, nonscaly alopecia with hairs broken off flush or near flush to the scalp (so-called black-dot ringworm), and (3) inflammation and induration of the scalp with associated hair loss that can progress, in extreme cases, to a kerion. Potassium hydroxide (KOH) preparation is less likely, especially in cases of inflammatory tinea, to be positive than a

culture: both should be done. A positive KOH generally demonstrates spores versus hyphae. The most common causative agent in the United States is *Trichophyton tonsurans*.

Treatment must be systemic, although 2.5% selenium sulfide shampoo* or 2% ketoconazole shampoo two to three times per week is an effective adjuvant that decreases shedding of viable spores. Griseofulvin (Fulvicin), in doses of 10 to 25 mg/kg given with a fatty meal (glass of milk) for at least 8 weeks is effective in most cases. Side effects are infrequent but include headaches, gastrointestinal disturbances, and photosensitivity. A fungal culture should be negative before discontinuation of treatment.

Ketoconazole (Nizoral)* is a much less effective drug for tinea capitis than griseofulvin. The triazoles, either fluconazole (Diflucan),* in doses of 5 to 6 mg/kg or itraconazole (Sporanox)* or terbinafine (Lamisil),* in a standard dosing regimen by weight (<20 kg = 62.5 mg/d, 20–40 kg = 125 mg/d, and >40 kg = 250 mg/d) are effective alternative treatments of tinea capitis when given daily for 4 weeks. Itraconazole can also be dosed at 3 to 5 mg/kg/d for 1 week, with repeat courses every 2 to 3 weeks for an additional 1 to 3 pulses. The triazoles have a greater potential for drug-drug interactions because they affect the cytochrome P-450 system. Household and other close contacts should be checked for simultaneous infection and treated: to not do so invites incomplete eradication or recurrence of infection in the proband.

*Not FDA approved for this indication.

CANCER OF THE SKIN

method of
LEONARD DZUBOW, M.D., and
EYAL K. LEVIT, M.D.

University of Pennsylvania
Philadelphia, Pennsylvania

Nonmelanoma skin cancers account for over a third of all cancers in the United States. They are the most common cancers among whites worldwide. Over 95% of these are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Their incidence is estimated between 0.9 and 1.2 million new cases per year. BCC accounts for 80%, with the remaining 20% being SCC.

The pathogenic mechanism is most likely related to the malignant transformation of keratinocytes in a monoclonal fashion. Damage to DNA, due to mutated tumor suppressor gene (especially high frequency of ultraviolet [UV] light-induced mutations of the *p53* tumor suppressor gene and/or activation of oncogenes as *ras* proto-oncogenes), if uncorrected, leads to the initiation of a "weakened" cell. On further exposure to carcinogens, months or years later, a second "hit" to the "weak" cell promotes the progression into a malignantly transformed cell. This theory is known as the "two (or multiple)-hit theory."

Today, as more carcinogens involved in the pathogenesis of skin cancer are identified, it is imperative that physi-

cians educate patients about their existence. A preventive approach through identifying premalignant skin cancers as actinic keratoses and informing patients about possible carcinogenic factors is important. A lag of about 20 years between the initial exposure to carcinogens and the appearance of clinically evident malignancy hinders such tasks. The use of a variety of products to halt the initiation or promotion of the "weakened cell" into a transformed malignant cell seems promising. Such products include antioxidants, corticosteroids, and free radical scavengers, such as vitamin C, vitamin E, selenium, and retinoids. These agents may help halt the initiation phase of tumor progression. The tumor promotion phase could be slowed by antiproliferative drugs or antioxidants such as protease inhibitors (e.g., leupepin*), as well as a diet high in retinoic acid, vitamin D, and green tea.

Once a skin cancer has appeared, definitive treatment is needed.

BCC is the most common skin cancer type, with incidence ranging from 1/100 in Australia and 146 to 317/100,000 in the United States. It usually affects middle-aged whites, although prepubertal lesions can appear in certain genodermatoses such as basal cell nevus syndrome, xeroderma pigmentosum, and albinism, among others. The most commonly involved sites are the head and neck. BCC is only locally aggressive, with rare metastases in less than 0.005% of patients (usually enlarged, ulcerated, and recurrent tumors). It is estimated that once a person has one BCC there is a 47% chance of developing a second unrelated BCC within 3.5 years.

Although UV radiation plays a major role in the formation of BCC, unlike SCC, it is not related to the cumulative UV dosage. This is evident by the fact that 20% of BCCs occur in non-sun-exposed areas. Celtic ancestry (red/blond hair and blue eyes) and family history of skin cancer independently confer an increased risk of skin cancer. Outdoor occupation appears to propagate skin cancer rather than be an independent risk factor. Although chemical carcinogens such as arsenic, ionizing radiation, immunization scars, chronic ulcers, and immunosuppression can lead to BCCs, they more often promote the formation of SCCs.

Recent keratin studies support the origin of BCC from the hair follicle (outer root sheath below the isthmus). This explains why BCC, unlike SCC, occurs only on hair-bearing skin. Clinically, BCC often resembles a "pimple" or a "pearly" telangiectatic cyst that lasts over a month. Other forms appear as red scaly plaques, scarlike patches, or even brown to black pigmented papules. They often bleed on trauma and may be associated with itching.

SCC of the skin is the second most common skin cancer. Its incidence has been increasing by 4% to 8% per year. It is directly related to the cumulative UV exposure, with UVB (290–320 nm) wavelength (mostly blocked by the ozone layer) more so than UVA (320–400 nm). This explains why over 70% of SCCs occur on the sun-exposed regions of the head and neck. The reported incidence is higher in men than in women. In the United States each year, 156 new cases are reported in men and 100 new cases are reported in women per 100,000 population. The rate in African Americans is much lower, being 3 per 100,000, and is associated with burn scars rather than UV exposure.

SCC commonly occurs in middle-aged whites. The incidence of metastasis from sun-induced SCC ranges from 0.5% to 25%. This is less than that from SCC arising in a chronic ulcer, scar, or radiation dermatitis, which is 18% to 38%.

Although only 6% to 10% of actinic keratoses progress into SCC, 60% of SCC arise from an actinic keratosis that had been present at least 1 year earlier.

SCC clinically appears as a red scaly patch or nodule, at times with central erosions or ulcerations. When located on mucosal surfaces such as the lips or genitalia, they may look like whitish or red nonscaly patches or plaques. When SCC is associated with HPV, it may appear as a fungating verrucous lesion.

TREATMENT OPTIONS

Factors that should be considered when choosing a treatment modality include skin cancer location, size and duration, histologic type, and previous treatment. Patients' concurrent medical conditions should also be considered.

The main disadvantage of the first four mentioned modalities is the lack of tissue for histologic conformation. The outcome is thus highly variable and correlates with the choice of cancer treated as well as the clinical skill and experience of the operator.

Cryotherapy

This is a method that uses heat removed from tissue by application of cold. The most common cryogen material used is liquid nitrogen with a boiling point of -195.8°C . The liquid nitrogen is typically delivered from either a spray bottle or by using a cotton-tipped applicator. A proper procedure includes a rapid freeze and slow thaw repeated twice with a minimum temperature of -50°C at the base of the tumor. Rapid cooling leads to intracellular ice formation with subsequent cell lysis during thawing.

Patients allergic to local anesthesia, with anticipated poor wound healing, or necessitating a bloodless method, are excellent candidates for cryotherapy.

If used as a treatment for skin cancers, it is advisable to use thermocoupling electrodes that ensure proper freeze at the base of the tumor. Although this method is indispensable for precancerous lesions as actinic keratosis and can be used with BCC in experienced hands, it is not advisable for use in SCC because it may hide residual cancer that has a metastatic potential.

Electrodesiccation and Curettage

This method uses a medium-sized curet (a looplike metal with a handle and sharp edge on one side of the loop) to debulk the skin cancer. It relies on the fact that most skin cancers produce a gelatinous-like matrix that can be differentiated from the normal, hard dermis. This is followed immediately by electrodesiccation using a high-frequency, high-voltage, low-amperage damped current, which results in approximately 1 mm of surrounding tissue distraction. This process is repeated two more times with a smaller curet used to explore the base and margins for possible pockets of tumor. The use of the electrodesiccation provides a 3-mm margin (1 mm per step) beyond the skin cancer. Because the method depends on the

*Not available in the United States.

differentiation of the soft tumor from the hard dermis it cannot be used for skin cancers that extend into fat. It is also very difficult to perform reliably over cartilaginous surfaces as the ear and nose. Because of the use of a current this method is better off avoided in patients with pacemakers, although the modern pacemakers are very well shielded from standard electrosurgical current. It should not be used in the perianal and oxygen enriched (close to a nasal canula) areas to avoid fire. The plume from the cautery is carcinogenic and may also carry viral particles.

In experienced hands a recurrence rate of less than 6% can be achieved for primary skin cancers that do not fit the criteria for Mohs surgery.

A resultant white, depressed, or hypertrophic scar may appear.

Radiation Therapy

This method uses ionizing radiation between 4000 and 7000 cGy, fractionated over 4 to 6 weeks, three to five times per week. We do not recommend this modality for patients younger than age 50 who are able to undergo one of the other-mentioned treatments because ionizing radiation is itself a nonselective DNA-damaging modality that can lead to future skin cancers. Depending on the location and fractionation, this may be a well-tolerated treatment with good to fair cosmetic results, albeit being time consuming.

Laser Surgery

Ablative surgery with laser resurfacing such as CO₂ or erbium:YAG is a blind technique that results in superficial burn. Although it may be used to treat precancerous lesions, it is not advised for the treatment of skin cancer because it may lead to an insufficient and superficial treatment, allowing a residual tumor to grow hidden beneath a scar.

Photodynamic therapy (PDT) is a modality that has been gaining acceptance in the treatment for bladder, esophageal, and lung cancer and, more recently, for superficial skin cancers and precancers. It uses the combination of a photosensitizer, which preferentially accumulates in malignant cells, and photoactivation by visible light to kill the tumor cells. The only currently Food and Drug Administration-approved chemical is photophrin, which is administered intravenously, costing over \$2000 and resulting in an undesirable, generalized photosensitivity for a period of 2 months. Stage three clinical trials are ongoing with the use of a topical photosensitizer (5-aminolevulinic acid). Whereas this topical medication will allow for fewer side effects, it will also result in decreased cure rate, owing to the physical limitation of the cream's penetration depth. In one study, 50% of skin cancer showed residual tumor, with the recurrence rate in another study over 16% within 2.5 years.

Surgical Excision

A 4- to 5-mm margin is recommended around a BCC or SCC. Using this method one usually removes the skin cancer in an elliptical fashion and sends the specimen for pathologic evaluation. Because of the method used by the laboratory to process the specimen, it is impossible to examine all edges of the specimen received. A "clear" margin, thus, does not necessarily ensure clear margins, resulting at best in a 95% cure rate offered by this method for primary skin cancers. The advantage of this method, aside from providing a specimen for pathologic evaluation, is the ability to reconstruct the surgical defect immediately.

Mohs Micrographic Surgery

This method allows a 99% cure rate of SCC and BCC. It involves removing the skin cancer initially with less than a 1-mm margin. The tissue is then processed keeping the orientation it had on the patient. The processing is done by frozen section to allow examination of all skin edges. The Mohs surgeon/pathologist examines the cut sections under the microscope and maps out the involved edges. This map is used as a guide to the edges needing further attention. The surgeon removes only the involved edges taking a millimeter of skin at a time in the direction of the involved edge. The process is repeated until negative margins are achieved. The advantage of this method is the ability to provide the highest cure while having the smallest surgical defect (corresponding as closely as possible to the size of the original skin cancer).

Mohs surgery is especially indicated for cancers of long duration, located on cosmetically sensitive regions of the body such as the face, with a history of recurrence, and located on the "H" region of the face (midface and ears, where other therapeutic modalities show a 9%–18% 5-year recurrence). A lesion of greater than 2 cm (has a 26% recurrence if removed by regular excision) or with aggressive histology (morpheaform, micronodular, infiltrative) (12%–30% recurrence with other treatment modalities) should also be referred for Mohs surgery. The previous use of radiation therapy as a treatment of the cancer also may increase the aggressive nature of the cancer and require a more precise tissue-sparing technique, as is offered by the Mohs surgery.

Emerging Alternative Therapies

Recently, a number of immune and differentiation modulating creams have been used for superficial skin cancers. Because no sufficient long-term follow-up is available, their efficacy is still to be proven. These creams are listed below:

1. Imiquimod (Aldara)* is a 5% cream invented for the treatment of anogenital warts. It works by

*Not available in the United States.

increasing interferon alfa locally, which in turn increases the TH1 (cell-mediated) immune response. It is currently in study for superficial BCC only. It is applied three times per week for a period of 8 to 10 hours (usually at night). Side effects are mainly irritation and/or ulceration. Although it shows promise, there is no long-term follow-up. Patients may also develop significant irritation and itching at the treatment site, with resultant poor compliance.

2. Tazarotene (Tazorac)* is supplied as a 0.1% or 0.05% gel. It selectively binds to the retinoid receptors involved in the promotion of epithelial differentiation. A recent study using 0.1% gel daily for 5 to 8 months showed 100% improvement (decrease in size); 80% clearance of superficial BCC, and less than 30% clearance of nodular BCC. The study was small and lacked a long-term follow-up. Similar side effects are seen as with imiquimode.

3. Isotretinoin (Accutane)*: As chemotherapy, an oral dose of 4.5 mg/kg/d for 8 months shows a 10% complete clinical and histologic remission of BCC. As chemoprevention, an oral dose of 0.5 to 1.5 mg/kg/d is used. No new tumors are seen during the treatment period. No remission of present BCCs is seen on a chemoprevention regimen. Once the chemotherapy or chemoprevention is stopped (usually due to side effects) there is a rapid appearance of BCCs or "rebound."

4. The use of interferon alfa-2b (Intron A)* can give a 50% to 80% cure rate.

5. A new cream investigated for lymphoma called Targretin† may show promise in skin cancer treatment.

6. Because BCC is thought to arise from hair, it would be interesting to see whether the incidence of BCC would decrease in patients getting laser treatment for unwanted hair.

*Not FDA approved for this indication.

†Investigational drug in the United States.

CUTANEOUS T-CELL LYMPHOMAS

method of

PETER W. HEALD, M.D.

Yale University School of Medicine
New Haven, Connecticut

BIOLOGY OF CUTANEOUS T-CELL LYMPHOMA

The immunologic protection of the skin has antigen-specific and nonspecific components. T cells regulate the specific arm of the skin's immune system. Cutaneous T-cell responses are the function of a subgroup of T cells (aptly named "cutaneous T cells") that express specific homing affinities for the skin. One of the molecular mediators of skin homing has been delineated. T cells that express the cutaneous lymphoid antigen (CLA) are found in cutaneous lymphoid infiltrates but not in lymphoid infiltrates of other tissues. In addition, the malignant cells of cutaneous T-cell lymphoma (CTCL) have been shown to express CLA. The

skin homing protein CLA binds to E-selectin. The latter is upregulated on endothelial cells in inflamed skin. Thus, the circulation contains a readily recruitable reserve of immune cells for skin-based reactions. After tethering to the endothelial cells, CLA expressing T cells migrate to the cutaneous site of inflammation. Cells can then reenter the circulation by way of the thoracic duct or in local lymph nodes. This model of cutaneous T-cell-based immunity explains why patients with this disease often have multifocal skin infiltrates with no readily detectable peripheral blood involvement.

Patients with CTCL present with inflammatory skin lesions of varying sizes, from 4 cm up to total-body erythroderma. One histologic finding is that the T-cell infiltrates will frequently show epidermotropism. Investigations have shown that while in the epidermis the malignant cells of CTCL often express markers of activation and cell division, implying that there is a crucial step in the life cycle of the cell occurring in the epidermis. Presumably the malignant cells traffic the same pathways as normal T cells, freely moving about the skin and the blood. Sophisticated molecular studies have demonstrated circulating malignant cells where routine staging tests reveal normal peripheral blood parameters. As immunologically active cells, the CTCL cells can produce cytokines that probably mediate the clinical findings of erythema, pruritus, and tissue and peripheral blood eosinophilia. As the disease progresses there are several changes that may occur. One is transformation to high-grade large cell lymphoma. This histologic change of the disease signals a much more aggressive course. Another is that normal immune cells senesce in the presence of the expanding lymphoma population. This incurs a state of immunosuppression from the disease and manifests itself as increased susceptibility to infection and second malignancies. The various components of the biology of CTCL: skin homing, activation in the epidermis, recirculation, cytokine production, immunosuppression, and transformation, all come to bear on the therapy of the disease. Undoubtedly, the varying degrees of these components in different patients create the clinical variants of CTCL.

STAGING

The goals of therapy are remission, palliation, and improvement of survival. Given the chronic nature of the disease, surrogate markers for survival are used in clinical trials. Tumor burden measurements and measures of palliation are the markers most commonly used. Skin score systems and health assessment questionnaires are the tools used to assess both discrete and global manifestations of the disease. The primary goal of therapy is to prolong life while an equally important goal is to improve the quality of life. Clinical studies of CTCL patients began initially to measure the quantity more than the quality of life, with the first meaningful data being the survival curves for different stages. The first staging of CTCL was done on the basis of skin involvement in a multicenter project by the Mycosis Fungoides Cooperative Group. This working group established a T staging system as shown in Tables 1 and 2. Patients are segregated by the degree of skin involvement and the type of lesion. Three stages were defined by surface area: less than 10% (T1), greater than 10% (T2), and T4 as erythroderma (generally believed to be >80% body surface area but without sharp margins). The other stage defined was T3, signifying the presence of tumors but not quantifying the number or body surface area involved. The strength of this staging system was that it segregated the patients into groups that differ in-