Abstract. The epidemic of nonmelanoma skin cancer (NMSC) continues, in part due to aging of the world’s population, the frequency of early childhood sunburns, and episodic intense recreational sun exposure as opposed to sun exposure related to outdoor occupations. A nonsurgical approach to selected skin cancers could potentially decrease the expense and morbidity of surgical treatment for NMSC. The increase of comorbid medical conditions in the elderly makes alternatives to surgical management preferable under certain circumstances. This review will discuss medical alternatives ranging from biologic response modifiers to COX-2 inhibitors to lifestyle modifications, as well as their roles in the management of NMSC. This preliminary information will expand to include more therapeutic options for NMSC in the future. Further clinical trials are needed to better elucidate possible alternative treatment strategies for NMSC.

Background

Skin cancer, the most common malignancy occurring in humans, accounts for one third of newly diagnosed cancers. One in five Americans will be diagnosed with skin malignancy in their lifetimes. Skin cancer is divided into two broad categories: melanoma and nonmelanoma skin cancer (NMSC). Compared with other malignancies, nonmelanoma skin cancer (NMSC) is associated with much less morbidity and mortality. NMSC is, however, far more common than all other cancers combined. The incidence of nonmelanoma skin cancers (NMSCs) was estimated at 1.3 million cases for the year 2000, and is increasing. This statistic is likely a gross underestimate because there is little formal reporting of NMSC. NMSC can cause local tissue destruction and disfigurement if left untreated, and also carries a risk of metastasis. The costs to society, both direct and indirect, to manage NMSC are staggering.

Basal cell carcinoma (BCC) is the most common malignancy in the United States and comprises 75% of NMSC. Squamous cell carcinoma (SCC) is the second most common skin cancer, accounting for 20% of cases of NMSC. The goal of treatment is complete eradication of the tumor with preservation of the surrounding structures in an aesthetically acceptable manner. Several treatment options, both surgical and nonsurgical, are available. Mohs micrographic surgery is the therapeutic gold standard for all NMSCs in terms of cure rates, margin control, and tissue conservation, however, surgical removal can also cause significant disfigurement and functional impairment. Alternatives to the surgical management of cutaneous malignancies may be preferred under certain circumstances. Some tumors may be multifocal, extensive, in cosmetically sensitive areas, or not amenable to simple surgical treatment. Significant scarring may result after surgical intervention, depending upon the location of the lesion, as in the case of small superficial BCCs on the shoulders and central chest treated with electrodesiccation and curettage or excision, which may produce hypertrophic scarring or spread scarring disproportionate to the initial size of the lesion. In addition, as the population of older people, who may have more surgical risk factors, continues to increase, a careful assessment of surgical risk factors will need to be taken into account both preoperatively and perioperatively for an increasing proportion of patients. Skin cancer incidence increases with age, as do other medical problems, but octogenarians and above with multiple medical problems may not always be optimal candidates for surgical intervention; thus, a nonsurgical option, may, on occasion, be a strong consideration as an alternative form of treatment.

Radiation therapy, chemotherapeutic agents, biologic response modifiers, retinoids, and cyclo-oxygenase inhibitors have all been utilized in the medical treatment of cutaneous malignancies. In addition, there is a growing scientific and anecdotal body of evidence regarding antioxidants, such that there may be a role for some dietary recommendations and herbal therapies in the management of skin cancers. This review article will discuss the various nonsurgical treatment options, with the exception of radiation therapy, for the treatment of NMSC, notably basal and squamous cell carcinoma. Radiation therapy, while still a commonly used and useful alternative to surgery, has been reviewed elsewhere and will not be discussed.
Topical Chemotherapy

To date, the most commonly studied topical chemotherapeutic agent has been fluorouracil (5-FU). 5-FU, a structural analog of thymidine that hinders thymidylate synthetase, interferes with DNA synthesis in dividing cells, resulting in cell death. The limited data to support its use in cancer therapy report better outcomes with SCC in situ and superficial BCC than with invasive SCC and BCC, most likely due to inadequate penetration beyond the epidermis. 10 The most valuable role of topical chemotherapy with 5-FU is its use in the management of actinic keratoses, the precursor lesions of SCC.7 A study by Mohs et al. mentioned disappointing results for the use of 5-FU without clinical and histologic follow-up to confirm tumor eradication.11 The data on the topical application of 5-FU is limited. Thus, 5-FU enjoys a popularity not substantiated by the literature.

Electrochemotherapy (ECT) is used to increase the concentration of chemotherapeutic agents within tumor cells. Exposing skin cancer cells to short bursts of electricity enhances cell permeability to chemotherapy. Intrallesional bleomycin in combination with an electrical pulse, demonstrated some efficacy in the treatment of BCC, according to one study.12 Other studies have reported limited success with intravenous cisplatin given as part of a standard chemotherapeutic regimen.13,14 The routine use of topical or intrallesional chemotherapy as the sole treatment modality for BCC or SCC is neither widely accepted nor commonly recommended.

Imiquimod

Imiquimod, an imidazoquinoline marketed as Aldara™, is the first novel synthetic agent of a new class of immune response modifiers. It promotes immunostimulation by binding to cell surface receptors such as Toll receptor 7 and stimulating the secretion of a multitude of cytokines (IL-1, TNFa, IL-6, IL-10, and IL-12).15 Indirectly, imiquimod favors the activation of a Th-1 cell-mediated immunity and has shown antiviral and antitumor effects in animal models. Recent evidence suggests that imiquimod induces apoptosis of keratinocytes via caspase-3 activation (one of the final mechanisms leading to apoptosis) and mitochondrial cytochrome c release.16,17

Originally licensed in 1997 for the treatment of external anogenital and perianal warts, imiquimod’s mechanism of action against condyloma is the induction of high levels of cytokines and interferons in the skin, particularly IFN-alpha and IFN-gamma.18 As genital warts and tumors are handled similarly by the immune system, there has been considerable enthusiasm for the application of imiquimod in the treatment of cutaneous neoplasia. BCC is responsive to intrallesional interferon but this treatment is cumbersome, has some systemic toxicity, and only yielded approximately 80% response rates in a multicenter clinical trial.19,20

Because of the literature supporting the use of interferon in the treatment of BCC it seemed likely that imiquimod, applied topically, would have some activity against BCC. With this in mind, Beutner and Geisse conducted an initial small pilot study that demonstrated significant activity of imiquimod against BCC. This pilot study determined that more research into the use of imiquimod in the treatment of BCC was warranted.21 Subsequent to this initial study, several more studies demonstrated substantial efficacy and safety for imiquimod in the treatment of superficial and nodular BCC.22–26 The most effective and least toxic dosing regimen for imiquimod was determined to be five times a week for a period of at least 6 to 12 weeks.22–24 Complete response rates for superficial BCC were greater than those for nodular BCC. The sizes of the tumors ranged from 0.5 to 2.0 cm² and did not include aggressive growth-pattern BCCs or tumors in the “H-zone” of the face. The side effects of imiquimod most frequently include application site reactions, with pruritus, tenderness, and burning being most commonly reported. One study seeking to address the dilemma of whether occlusion of the skin after imiquimod application would enhance efficacy did not show any increased benefit in the management of superficial or nodular BCC.25 Additionally, in the authors’ experience, occlusion of imiquimod often produces unacceptable cutaneous side effects. There is a positive association between dosing frequency and the response rate, as well as the occurrence of sometimes severe local cutaneous side effects.22 BID dosing or daily dosing may increase the likelihood of local side effects and are not usually recommended. It is evident that decreased frequency of imiquimod application does enhance the tolerability to the patient, which may result in greater compliance.

Imiquimod has also been used off label to treat other types of nonmelanoma skin cancers. There have been multiple published case reports and small series documenting imiquimod’s utility in the treatment of squamous cell carcinoma in situ, Bowenoid papulosis, extramammary Paget’s disease, melanoma in situ, cutaneous metastases of melanoma, keratoacanthoma, and others.27–35

Imiquimod is a promising, patient applied, topical therapy for a number of cutaneous malignancies and offers a potential non-surgical approach in the management of selected cases of NMSC. Although the immune response modifiers are potent and fascinating drugs, the body of literature to support their use in the treatment of NMSC is very limited with the exception of the use of imiquimod for selected BCCs of the trunk. Since there are many compounds related to imiquimod, the future may be bright for this class of drugs in the treatment of NMSC.
Retinoids

Derivatives of vitamin A, retinoids are evolving as potential tools in the prevention of new BCCs and SCCs. Isotretinoin (13-cis-retinoic acid) is considered the most effective retinoid for the prevention of nonmelanoma skin cancer. Topical tretinoin has been shown to decrease the number of solar keratoses and may help prevent their progression to carcinoma. Current theory suggests that the retinoids’ mechanism of action involves the tumor-promotion phase of carcinogenesis by inducing apoptosis, impeding proliferation, and stimulating differentiation or a combination of these processes. Research is currently focused on the development of receptor-selective retinoids in the chemoprevention of NMSC. Originally developed for the topical treatment of plaque psoriasis, tazarotene, a receptor-selective retinoid for retinoic acid receptors (RARs), has shown some positive responses after daily application to BCCs for several months. This was preliminary data and no long-term results have been published to date. In addition, a recent one-year randomized study of renal transplant patients with systemic acitretin revealed a decrease in the number of actinic keratoses with no change in the incidence of new cutaneous malignancies. Despite promising results, the high rate of adverse events does not justify the routine use of retinoids in renal transplant patients. The response of established tumors to retinoids has been disappointing although some remissions have been reported. Side effects, particularly mucocutaneous dryness, are often dose limiting. Although retinoids may be successfully used as prophylactic agents when select transplant patients develop innumerable and rapidly progressive NMSC, the full potential of retinoids in the management of cutaneous neoplasia has not been fully realized.

Cytokines

Cytokines play a pivotal role in the immune system by modulating the development and function of humoral or cell-mediated responses to self or foreign antigens. Intralational injection of interferon (IFN) has shown some positive effects in the treatment of NMSCs as mentioned above. Interferons, especially alfa 2a and 2b, are strong inhibitors of malignant cell growth and have demonstrated effectiveness, both individually and as combined agents, in the treatment of BCCs. Greenway et al first documented a 100% success rate in a pilot study using intralational interferon alone for eight cutaneous BCCs. This high cure rate was not borne out after being subjected to larger studies.

The mechanism of action of interferon-alpha in the management of BCC has been partially clarified. IFN-alpha-treated BCCs express not only CD95 ligand but also CD95 receptor, and develop a favorable apoptotic environment via the CD95ligand-CD95 receptor interaction. Furthermore, data suggests that untreated BCC produces CD95 ligand constitutively, not the CD95 receptor, to outmaneuver an immune response from CD95 receptor-positive CD4+ T cells. CD95 receptor, a cell surface molecule, belongs to the TNF receptor superfamily. In addition, treatment of BCC with IFN-alpha stimulates the upregulation of interleukin-2 and the inhibition of IL-10 production, thereby inducing tumor regression. IL-10 is known to have inhibitory effects on cell-mediated immune responses, enabling cancers to evade the immune surveillance. In mycosis fungoides, low-dose IFN-alpha in combination therapy has shown a decrease in circulating malignant T-cells with cutaneous improvement. Potential side effects from IFN-alpha therapy include headache, fever, myalgia, and leukopenia. Interferon, while still used in some clinical settings, currently has limited usefulness as monotherapy for NMSC.

COX-2 inhibitors

Cyclooxygenase (COX), the rate-limiting enzyme for the production of prostaglandins (PG) from arachidonic acid, exists in at least two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed while COX-2 expression is induced by inflammatory stimuli, such as ultraviolet light exposure. Increasing evidence is pointing to the role of COX-2 and its products, notably prostaglandin E2, in the development of NMSC. Overexpression of COX-2 has been revealed in various neoplasms ranging from colorectal cancer to breast cancer, as well as skin cancer. Normal skin has minimal levels of COX-2 and PGE-2, with levels of COX-2 increasing in correlation with the severity of skin tumors from premalignant actinic keratosis to squamous cell carcinoma. Studies have shown positive results with NSAIDs for the treatment of cancer by inhibiting angiogenesis and stimulating apoptosis mainly via COX-2 inhibition. However, the nonspecific inhibition of COX-1 and COX-2 by NSAIDs leads to side effects associated predominantly with COX-1 inhibition, such as gastrointestinal ulcers and/or decreased renal function. Selective inhibition of COX-2 is preferable to nonselective inhibition, because it selectively reduces cancer cell proliferation with minimal damage to the gastrointestinal tract. A specific cyclooxygenase-2 (COX-2) inhibitor, celecoxib, has shown potential therapeutic benefit in the prevention of cutaneous neoplasia. Oral and topical celecoxib have demonstrated a chemopreventative effect in animal studies by inhibiting new tumor formation and delaying tumor latency. These COX-2 specific inhibitors are promising agents in the battle against cutaneous neoplasia. Further double-blinded, randomized, placebo-controlled trials in humans are warranted to define the role of
celecoxib and other COX-2 inhibitors in the prevention and treatment of NMSC, as well as their possible side effects.

**Dietary and Herbal Supplements**

There is a growing interest in the use of dietary and herbal supplements for the prevention and treatment of cutaneous neoplasia. There may be potential usefulness for these vitamins in sunscreens, and many products are now on the market that combine antioxidants and sunscreens. The administration of antioxidants in combination seems to provide greater efficacy than protection by any single antioxidant in mouse models.

Evidence suggests that beta-carotene supplementation reduces UV-induced photoimmunosuppression, however, in a larger randomized, placebo-controlled study, there was no decrease seen in the incidence of NMSC with daily oral beta-carotene intake. Some reports have documented an increase in the minimal erythema dose with a synergistic combination of vitamins C (ascorbic acid) and E (d-alpha-tocopherol) oral supplementation. Other study involving patients with Fitzpatrick skin type II or III demonstrated significant benefit in reduction of UV-induced erythema with a topical combination of vitamin C, vitamin E, and melatonin. In a murine model, vitamin E has shown to prevent UV-induced thymine dimer formation and immunosuppression.

In addition, a high intake of dietary fat reduced the time span from UV exposure to the development of skin cancer. Patients randomly assigned to a low-fat diet intervention group demonstrated a significant reduction in the incidence of actinic keratosis after 8 to 12 months, while patients on the high-fat control diet had a five times greater risk of developing an actinic keratosis. Dietary modification with respect to a low-fat diet could serve as a potentially important intervention in the prevention of non melanoma skin cancer (NMSC).

1,25-dihydroxyvitamin D3 analogs, such as CB1093, may also play a role in the medical management of early melanoma. Aside from water, tea is the most common beverage consumed worldwide, especially in China and India. There is a growing body of evidence that polyphenols from black and green tea exhibit inhibitory properties against UV-induced photocarcinogenesis in animal models. Recent findings suggest that procyanidins, notably procyanidin B5-3’-gallate, isolated from grape seeds exert antioxidant activity against UV-induced photodamage. Further randomized, double-blind, placebo-controlled trials are required to better elucidate the positive benefits of diet and herbal therapy in the treatment of cutaneous neoplasia.

**Conclusions**

The encyclopedia of nonsurgical therapies is still being expanded for the management of nonmelanoma skin cancer. Different chapters of the encyclopedia will be utilized more often than others depending on the severity, location, and other circumstances of each individual patient afflicted with NMSC. Although medical management is even now an effective and sometimes preferable strategy for selected cases, further trials are warranted to develop better guidelines for its use in cutaneous neoplasia. Because nearly 20% of Americans will suffer from NMSC in their lifetimes, noninvasive therapeutic options will become increasingly important as their mechanisms of action and efficacy become better elucidated.

**References**


