Nonsurgical Modalities of Treatment for Primary Cutaneous Cancers

71

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Contents

Abstract

Skin cancer, including melanoma and nonmelanoma skin cancers (NMSCs), is the most common malignancy affecting humans. The incidence of these cutaneous malignancies increases with age, making the elderly population most prone to the development of these cancers. Although surgery is usually the treatment of choice for cutaneous malignancies, it may not be the most appropriate solution. Not only does surgery cause major disfigurement and functional impairment, but also the patient may be a poor surgical candidate, necessitating use of other modalities of treatment. The choice of the treatment modality to be utilized should be tailored according to specific cancer characteristics (type, size, location) and patient factors (age, comorbidities, use of multiple drugs, including anticoagulants). This is especially true if elderly patients have an increased incidence of other medical comorbidities that may have an adverse effect on surgery. In such circumstances, alternatives to surgery may be the preferred choice. This chapter aims at reviewing the currently available evidence on the various nonsurgical therapeutic modalities for the different types of skin cancer. These include topical, intralesional, and systemic treatments, as well as physical treatment modalities. Furthermore, certain dietary and herbal supplements may also have a role in the prevention of skin cancers.

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Introduction

Skin cancer, which includes melanoma and nonmelanoma skin cancers (NMSCs), is the most common malignancy affecting humans [1–4]. Basal cell carcinoma (BCC) represents the most common cutaneous malignancy (comprising approximately 75 % of NMSCs), followed by squamous cell carcinoma (SCC), which comprises around 20 % of NMSCs [1–4]. The incidence of these cutaneous malignancies increases with age, making the elderly population most prone to the development of these cancers [1–4].

Although surgery, particularly Mohs micrographic surgery, is usually the treatment of choice in the management of cutaneous malignancies in terms of margin control and cure rates, it may not be the most appropriate solution because of its disadvantages [1–4]. The choice of the treatment modality to be utilized should be tailored according to specific cancer characteristics (such as type, size, location) and patient factors (age, comorbidities, use of multiple drugs, including anticoagulants) [1–4]. Not only does surgery cause major disfigurement and functional impairment, but also the patient may be a poor surgical candidate, necessitating use of other modalities of treatment [1–4]. This is especially true in elderly patients who are not only characterized by an increased incidence of cutaneous malignancies but also by an increased incidence of other medical comorbidities that may have an adverse effect on surgery [1–4]. In such circumstances, alternatives to surgery may be the preferred choice.

The chapter aims at reviewing the currently available evidence on the various nonsurgical therapeutic modalities for the different types of skin cancer. These include topical, intralesional, and systemic treatments, as well as physical treatment modalities. Furthermore, certain dietary and herbal supplements may also have a role in the prevention of skin cancers.

Topical Therapies

Several topical agents have been used in the treatment of cutaneous malignancies, including imiquimod, 5-fluorouracil, tazarotene, ingenol mebutate, diclofenac, and cidofovir [1–4]. The use of these agents should be guided by evidence on their effectiveness in the treatment of specific types of skin cancers, patient profile, and the medication's side effects. The use of topical agents has several advantages such as ease of use, convenience (as the medication can be applied at home), and ability to treat larger lesions and critical sites and may usually lead to better cosmetic outcomes. However, several disadvantages should be noted, the most important of which is the initial irritating inflammatory response, which can affect patient's compliance and subsequently the final results. In addition, the expensive cost of some of these agents (such as imiquimod) may limit its use.

Imidazoquinoline Compounds (Imiquimod and Resiquimod)

Several studies have shown that the mechanism of action of imidazoquinoline compounds (imiquimod and resiquimod) as immunomodulators is mediated by the activation of Toll-like receptors 7 and 8 (TLR7, TLR8), which leads to the production of interferon-alpha (IFN-a) and other cytokines, including interleukin (IL)-12 and IL-18 [1, 5]. These then mediate the antitumoral effect through their enhancement of the cell-mediated immunity. Also, the antitumoral effect is mediated through upregulation of the opioid growth factor receptor (OGFr) that, in turn, stimulates the interaction of the OGF–OGFr axis, which is an inhibitory pathway regulating cell proliferation [6].

There is now plenty of evidence on the effectiveness of the imiquimod 5 % cream in the treatment of multiple primary cutaneous malignancies. Currently, it is US Food and Drug Administration (FDA) approved for the treatment of superficial BCCs (especially those that are smaller than 2 cm on the trunk, neck, or extremities) and actinic keratoses (AKs) [1, 2, 5].

Different studies have shown that the rate of clinical and histological clearance of superficial BCCs treated with imiquimod 5 % cream (applied

5 or 7 days/week for 6–12 weeks) is greater than 90 %. Although less evidence based, the use of imiquimod in the treatment of nodular BCCs has also proven to be effective (clearance rate ranged between 70 % and 100 % based on different studies) [1, 2, 5].

As in the case of superficial BCCs, imiquimod is also FDA approved for treating AKs of the head and neck region. This has been supported by several studies that have shown a 50 % complete clearance rate of AKs (compared to 5 % of AKs in patients treated with placebo) that were treated with imiquimod 5 % cream (applied 3 days/week for 12–16 weeks) [1, 2]. Recently, a new standard for AK management has been set with the target being detection and clearance of clinical and subclinical AKs across the entire sun-exposed field. This concept has used imiquimod 3.75 % cream (daily on two 2-week treatment cycles that are separated by a 2-week treatment-free interval) and reduction in lesions from Lmax (maximum lesion count during treatment). This treatment resulted in 92 % median percentage reduction in AK lesions with sustained lesion clearance for at least 1 year and acceptable tolerability profile [7]. Based on these data, imiquimod 3.75 % was suggested as a first-choice treatment for patients with AK.

Although there is currently less evidence supporting the use of topical imiquimod in the treatment of other skin malignancies – including Bowen's disease or squamous cell carcinoma in situ (SCCIS), invasive SCC, or lentigo maligna – anecdotal reports and small studies have shown that imiquimod may be quite effective [1, 2]. This can thus be used in those patients who are poor surgical candidates.

Adverse reactions most commonly encountered with the use of topical imiquimod include erythema, ulceration, edema, and/or scaling, and these are usually limited to the application site. These reactions can be intense, especially with increased application frequency and especially in patients being treated for AK or BCC [1, 2, 5]. Flu-like symptoms such as fever, fatigue, and myalgias are systemic adverse effects that have been reported in approximately 1–2 % of patients.

5-Fluorouracil (5-FU)

The mechanism of action of 5-FU derives from it being a structural analog of thymine. 5-FU acts as an antimetabolite and interferes with DNA synthesis by inhibiting thymidylate synthetase. It acts mainly on rapidly dividing cells such as tumor cells [1–4].

First used in clinical practice in the 1960s, topical 5-FU is now present in different formulations including solutions (1 %, 2 %, and 5 %) and creams (0.5 %, 1 %, 2 %, and 5 %). They are approved by the FDA for the treatment of AKs. The 5 % cream has been approved by the FDA for treating superficial BCCs. Its effectiveness in the treatment of AKs has been shown to be comparable to imiquimod [1, 2]. Anecdotal reports have also shown that 5-FU may be effective in the treatment of SCCIS [1]. The usual application regimen is once or twice daily for up to 4 weeks.

Adverse reactions commonly described with the topical use of 5-FU include local irritation, allergic contact dermatitis, pain, erythema, edema, pruritus, dyspigmentation, and photosensitivity [1–4]. Uncommon reactions such as onychodystrophy and the appearance of telangiectasias may also occur. Rarely, systemic absorption may lead to systemic side effects such as nausea, myelosuppression, diarrhea, cardiac abnormalities, and neurologic toxicity [1–4].

Tazarotene

Tazarotene is a third-generation retinoid that usually exerts its effect on keratinocyte differentiation and proliferation, mainly through its interaction with RAR-β and d receptors [1]. However, the underlying mechanism of its confirmed effect in the treatment of NMSCs in a few small studies is still not well understood [1].

One study showed that the daily use of 0.1 % tazarotene gel for the treatment of BCC resulted in a complete clearance rate of 53 %. The duration of treatment in this study ranged between 5 and 8 months [1]. Similarly, 0.1 % tazarotene gel used daily for up to 6 months in the treatment of SCCIS resulted in a clearance rate of 47 % [1].

Like the other topical retinoids, the most common adverse reaction observed with tazarotene is skin irritation, manifesting in the form of redness, scaling, dryness, and pruritus, in addition to a burning, stinging sensation. This reaction tends to be most severe during the first weeks of therapy, with gradual recession later on [1]. Other less common adverse effects include dyspigmentation and allergic contact dermatitis.

Ingenol Mebutate

Ingenol mebutate is a macrocyclic diterpene ester and a natural extract from the sap of *Euphorbia peplus*. It has a dual mechanism of action: induces rapid cell death that occurs few hours after application and also elicits an inflammatory response within days that eliminates residual tumor cells [8, 9]. Two formulations are available and FDA approved for AKs. A 0.015 % gel for the face and scalp is applied once daily for 3 days and may cover a 5 × 5 cm surface area. A 0.05 % gel is used for the trunk and extremities once daily for 2 days. It offers the advantage of increasing compliance because it is applied for a short period of time. Phase 3 trials on efficacy showed that the proportion of patients who achieved complete clearance (100 %) and partial clearance (>75 %) of AKs on the face or scalp was significantly higher with ingenol mebutate than with vehicle: 42.2 % versus 3.7 % and 63.9 % versus 7.4 %, respectively, ($P < 0.001$) [8, 9]. In the studies of AK on the trunk or extremities, results for the primary end point of complete clearance also demonstrated significantly higher clearance rates with ingenol mebutate versus vehicle: 34.1 % versus 4.7 % ($P < 0.001$). Partial clearance rates (ingenol mebutate versus vehicle, 49.1 % versus 6.9 %; $P < 0.001$) and median lesion count reduction (ingenol mebutate versus vehicle, 75 % versus 0 %) were significantly higher for ingenol mebutate than for vehicle and confirmed the efficacy of ingenol mebutate for the treatment of AK on the trunk or extremities.

Adverse effects include erythema, scaling, crusting, pruritus, infection, blister formation, postulation, erosions, and ulcerations [8, 9]. They are usually transient and healing occurs within 2–4 weeks of application.

Other Topical Agents

Case reports and small studies have also documented the effect of other topical agents such as cidofovir and diclofenac in the treatment of cutaneous malignancies [1].

In one study, cidofovir, which is a purine nucleotide analog of deoxycytidine, resulted in a 75 % clearance rate of BCC when used as a 1 % cream applied daily over a period of 2 months [1]. No significant side effects were observed in the study, and the treatment was well tolerated by patients. The underlying mechanism of action of cidofovir is thought to be an antineoplastic and antiangiogenic effect.

Diclofenac, a nonsteroidal antiinflammatory drug (NSAID), usually exerts its antitumor effect through the inhibition of the cyclooxygenase (COX II). This is believed to inhibit angiogenesis and tumor invasion, leading to a decrease in the rate of epithelial tumor growth. One double-blind, placebo-controlled study showed that twice-daily diclofenac application in the form of a 3 % gel resulted in a 33 % complete clearance of AKs [1]. Local irritation was observed as a side effect, but was much less severe than that observed with either 5-FU or imiquimod [1].

Intralesional Agents

Multiple agents in an intralesional form have proven their efficacy in the management of cutaneous malignancies, including bleomycin, 5-FU, and interferon-a (IFN-a) [1, 10, 11]. Advantages of this form of therapy include the ease of delivery, the ability to use it as an adjuvant treatment to surgery, and good cosmetic results in general. Disadvantages include the currently sparse amount of evidence supporting their use, their high costs, and the usual need for multiple treatment sessions [1, 10].

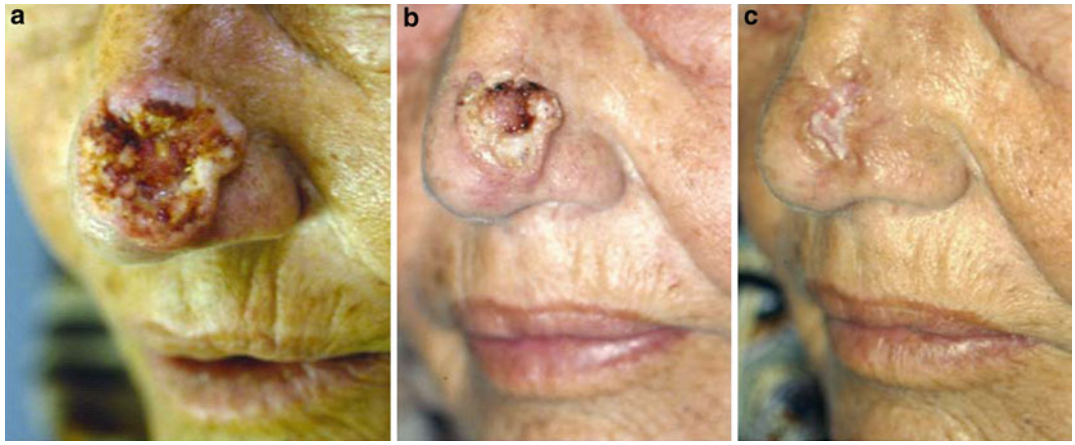

Fig. 1 Elderly woman with keratoacanthoma over the nose treated with intralesional IFN-a: (**a**) before treatment, (**b**) after one injection, and (**c**) after two injections

Bleomycin

Several mechanisms mediate the antitumor effect of bleomycin, a cytotoxic antibiotic produced by *Streptomyces verticillatus*, including its inhibition of DNA ligase preventing repair of DNA, its effect on the G2 and S phases of the cell cycle of fast-dividing cells resulting in SS DNA breakage, and promotion of apoptosis and epidermal necrosis [1, 10].

Individual case reports have described the efficacy of intralesional bleomycin in the treatment of BCCs and keratoacanthomas [1, 10]. Adverse effects that have been described with the intralesional use of bleomycin include local pain, swelling, dyspigmentation, ulceration, superficial scarring, flu-like symptoms, and, rarely, flagellate hyperpigmentation [1, 10].

5-Fluorouracil

There is now evidence that 5-FU as an intralesional preparation can be quite effective in the treatment of BCC, SCC, and keratoacanthomas [1]. In one study, intralesional injection of 0.5 mL of 5-FU/epi gel three times weekly for 2 weeks resulted in 100 % clearance of BCCs. Another study on the treatment of SCCs showed that 1.0 mL weekly injection of 5-FU/epi gel for up to 6 weeks achieved a 96 % clearance rate.

Although excellent cosmetic results may be achieved with its use, intralesional 5-FU may be locally complicated by pain, erosion, ulceration, and dyspigmentation [1].

Interferon-a (IFN-a)

Intralesional interferon-a (IFN-a) can be quite effective in the treatment of keratoacanthomas (Fig. 1), BCCs, and SCCs [1, 2, 11]. This effect of IFN-a is thought to be mediated by the enhancement of cell-mediated immunity against malignant cells through increasing the antigen-presenting cell function, stimulating the activity of natural killer cells, and promoting the development of T-helper (Th)-1 response while at the same time suppressing the production of Th-2 cytokines [1, 11].

One study showed complete clearance of all BCCs and SCCs that were treated with intralesional IFN-a given in a dose of 1×10^6–2×10^6 IU three times weekly for 3 weeks. Adverse reactions most commonly encountered with the use of IFN-a include flu-like symptoms and local injection-site

reactions. Laboratory abnormalities may also be observed, such as elevation in hepatic transaminases and decrease in white blood cell count [1, 11]. Given that the relative contraindications for the use of IFN-a include a history of cardiovascular, renal, hepatic, or central nervous system disorders, its use in the elderly population should be undertaken with extra caution, as these patients usually have multiple comorbidities.

Systemic Agents

A problem in treating transplant patients is to provide effective immunosuppression while at the same time not promoting cancer development. Mammalian target of rapamycin (mTOR) inhibitors have both immunosuppressive and tumor-suppressive functions [12].

For the most part, there are insufficient data to draw clear conclusions on the effectiveness of mTOR inhibitors against cancer in humans. However, there are hints that these drugs may be very useful in transplant recipients. Multiple groups have reported on calcineurin inhibitor (CNI)-immunosuppressed renal transplant recipients with Kaposi's sarcoma, demonstrating tumor regression after switching from CNIs to sirolimus, which is an mTOR inhibitor [12]. Tumor regression occurred in the face of full immunosuppression with sirolimus, thus not increasing the risk for organ allograft rejection.

Physical Modalities of Treatment

Many treatment modalities fall under this category, including cryotherapy, electrodessication and curettage (ED&C), radiotherapy, photodynamic therapy (PDT), and laser ablation [1, 2]. Most of these have plenty of evidence to support their use, with each of them having its advantages and disadvantages.

Cryotherapy

Cryotherapy has historically been the classical alternative treatment for cutaneous malignancies when surgery is not an option. There is now plenty of evidence to support the use of cryotherapy in the treatment of AK, SCCIS, and BCC (Fig. 2) [1, 2, 13]. It is suitable for the treatment of single or multiple tumors, especially in patients who are old, debilitated, using pacemakers, or maintained on anticoagulation [1, 2, 13]. Excellent cure rates, ranging from 97 % to 99 %, have been achieved upon treatment of these different tumor types with cryotherapy; however, cryotherapy is usually associated with higher recurrence rates (reaching

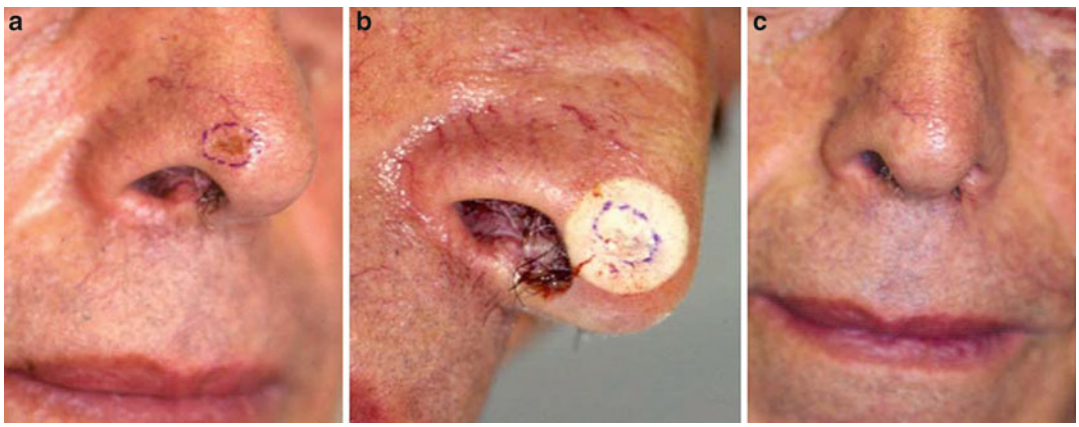

Fig. 2 Elderly man with BCC over the nose treated with cryotherapy: (**a**) before treatment, (**b**) during treatment, and (**c**) after treatment

up to 17 %) and poorer cosmetic outcomes when compared to surgery or PDT [1, 2, 13]. In order to ensure successful outcome, malignant lesions should generally receive cryotherapy until a clinical freeze margin of 5 mm is observed [1, 2, 13].

The major advantage of cryotherapy is its convenience and ease of use in regular dermatology offices [1, 2, 13]. Treatment of AK is usually achieved with one freeze–thaw cycle of 5–7 s, while SCCIS and BCC should be treated with two freeze–thaw cycles of approximately 40–90 s each, aiming at a temperature of −50 °C to −60 °C at the base of the lesion [1, 2, 13].

Cryotherapy is contraindicated in patients with a history of Raynaud's phenomenon, cold urticaria, or cryoglobulinemia, as well as in treating deeply penetrating or aggressive tumors or those characterized by indistinct or ill-defined borders [1, 2, 13].

Electrodesiccation and Curettage

ED&C is another physical destructive therapeutic modality that has proven its efficacy in the treatment of different NMSCs, including BCC, SCCIS, and SCC [1, 2, 14]. In order to achieve high cure rates with ED&C, selection of the appropriate patient, with low-risk tumor characteristics, is of paramount importance. Relative contraindications for treatment with ED&C include immunocompromised patients, high-risk locations (such as nose, ear, or periorificial areas), a tumor size larger than 2 cm, recurrent lesions, and an aggressive histological tumor subtype [1, 2, 14]. The evidence has mainly been provided by large retrospective studies, which showed that treatment with ED&C achieves cure rates in the range of 74–100 % for BCCs and 96–100 % for SCCs [1, 2]. Recurrence rates of BCCs treated with ED&C are comparable to surgical excision and range between 3.3 % and 5.7 % for primary BCCs less than 1 cm in size [1, 2]. Compared to cryotherapy in the treatment of SCCIS, ED&C is characterized by lower recurrence rates and shorter healing times [1, 2]. Combining ED&C with topical treatments such as imiquimod cream has been shown to have a synergistic effect, resulting in better tumor clearance and improved cosmetic outcome [1, 2].

ED&C has the advantages of being a valuable, efficient, cost-effective tool that could be the ideal alternative to surgery in the management of cutaneous malignancies, especially in a patient who is a poor surgical candidate [1, 2, 14]. Compared to surgery, the cosmetic outcome after ED&C is usually inferior. The disadvantage of ED&C includes the inability to confirm tumor clearance histologically. Adverse effects observed with the use of ED&C include dyspigmentation and hypertrophic or atrophic scars [1, 2, 14]. Patients with cardiac pacemakers are better managed by electrocautery instead of electrodesiccation/coagulation [1, 2].

Radiotherapy

Radiation represents another important alternative to surgery in the treatment of BCCs and SCCs, especially in elderly patients or those having major medical comorbidities or large-sized inoperable tumors [1, 2]. Although the use of radiotherapy has declined in recent years in order to avoid detrimental side effects of radiation and because of the appearance of better and less harmful modalities of treatment, radiotherapy can still be of significant value in the treatment of medium-sized (1–4 cm in diameter) cutaneous malignancies occurring on the face of older patients [1, 2]. Smaller malignancies are better managed with surgery, while larger tumors are better treated with a combination of surgery and radiation or by Mohs surgery [1, 2].

Radiotherapy of cutaneous cancers can usually be done using grenz rays or soft or superficial x-rays. Preservation of surrounding normal tissue is usually possible when using radiotherapy for cutaneous malignancies, because the radiation doses required for cancer eradication are not that highly damaging [1, 2]. The major advantages of using radiotherapy include preservation of normal uninvolved tissue (especially for large tumors or those in difficult locations), minimal patient discomfort, the ability to be performed on outpatient basis, and the ideal alternative to surgery in the

treatment of elderly patients who are poor surgical candidates or who are physically or psychologically handicapped [1, 2]. While radiotherapy is considered to be curative for lentigo maligna, BCC, SCC, and keratoacanthoma, its use for the treatment of invasive melanoma, Kaposi's sarcoma, and lymphomas is only palliative [1, 2].

Contraindications for the use of radiotherapy include chronic radiodermatitis, verrucous carcinoma, previously irradiated cutaneous malignancies, genodermatoses such as xeroderma pigmentosum, intraoral tumors, tumors penetrating into the cartilage or bone, and those found in scars of burns, chronic leg ulcers, or osteomyelitis [1, 2].

Although several studies have shown that radiotherapy may be comparable to surgery in the clearance rate achieved for the treatment of different cutaneous malignancies (BCC, SCCIS, keratoacanthoma, SCC), the former is usually associated with higher recurrence rates [1, 2]. A 5–15 % 5-year recurrence rate occurs when radiotherapy is used for BCC and SCC treatment.

Radiotherapy can also be utilized for the treatment of recurrent cancers when surgery is not an option, or it can complement (adjuvant to) surgery in treating lesions (both BCCs and SCCs) that cannot be completely removed by surgery due to their size or location [1, 2]. Another excellent indication for radiotherapy is a large lentigo maligna, in which the results can be at least as good as those achieved with surgery; however, cosmetic outcomes are usually better in such cases with radiotherapy than they are with surgery [1]. BCCs, SCCs, and keratoacanthomas are best treated with soft or superficial x-rays, and the regimen can be variable (a typical course would be a 2–4-Gy daily dose for up to 20 days) [1, 2]. Classical treatment for lentigo maligna includes the use of five to ten doses of 10–20-Gy grenz rays depending on the lesion size [1].

There are early and late adverse effects in the use of radiotherapy. The former include transient erythema and desquamation, while the latter include hypopigmentation, telangiectasia, atrophy, and fibrosis. Although this may indicate that radiotherapy leads to worse cosmetic outcomes than surgery, radiotherapy may actually achieve better cosmetic results than surgery for tumors in special locations, such as the lower lip, nasal tip, nasal ala, and eyelid [1, 2].

Photodynamic Therapy

Not only is topical photodynamic therapy (PDT) being widely used for the treatment of AKs, but plenty of evidence is currently accumulating to support the use of PDT in the treatment of NMSCs [1, 2, 15, 16].

In PDT, a photosensitizing compound, such as 5-aminolevulinic acid (ALA) and the methyl ester of ALA (mALA), applied to the skin gets converted to protoporphyrin IX upon absorption. Protoporphyrin IX then preferentially accumulates in the intracellular membranes of organelles, such as lysosomes and mitochondria, within the tumor cells. Upon activation by a light source in the 417,750-nm wavelength range, protoporphyrin IX goes into a higher energy state, leading to the generation of reactive oxygen species (including singlet oxygen), which damage and induce apoptosis of tumor cells [1, 2, 15, 16].

Most studies on topical PDT have been done to test its effectiveness in the treatment of AKs, and these have shown that the clearance rates (up to 90 %) are similar or maybe even better than those achieved with cryotherapy or 5-fluorouracil [1, 2].

Studies on BCCs have shown that PDT achieved results comparable to cryotherapy in the treatment of superficial BCCs as also comparable to simple excision in the treatment of nodular BCCs (complete responses in up to 90 %), although the recurrence rates were slightly higher with PDT [1, 2, 15, 16]. However, the cosmetic results are usually better with PDT than with either cryotherapy or surgery [1, 2, 15, 16]. This is because the damage is limited to the tumor cells of epithelial origin that get preferentially sensitized, while surrounding tissues are usually not affected as much. PDT is also effective in treating SCCIS, with one study showing a complete response rate of 88 %. Other cutaneous tumors, such as pigmented morpheaform or infiltrative variants of BCC and metastatic melanoma, are considered to be poor responders to PDT [1, 2].

Common adverse effects observed with PDT include stinging, itching, and burning during treatment, subsequently followed by erythema and edema [1, 2, 15, 16].

Laser Therapy

Ablative lasers such as the carbon dioxide (CO2) or erbium:yttrium–aluminum–garnet (erbium:YAG) vaporize tissue reaching to the level of the papillary dermis. By controlling the depth of injury, we may reduce the risk of scarring and the risk of permanently altered pigmentation [1, 17]. When considering treatment of cutaneous malignancies with laser ablation, the physician should consider the type of malignancy, as well as its location and the skin phototype of the patient. The advantages of using laser ablation in the treatment of primary cutaneous malignancies include the ability to treat large surface areas, the hemostatic nature of the procedure, the prophylactic effects, and the added potential cosmetic result of rejuvenation [1, 17]. Disadvantages include risk of scarring, expensive costs of the procedure, and the inability to treat hyperkeratotic or elevated lesions. Several studies have shown that laser ablation is quite effective in the treatment of AKs (reducing the number of AKs by up to 94 %), superficial and nodular BCCs (up to 97 % clearance), and SCCIS [1, 17]. However, laser ablation should not be used for thick hyperkeratotic lesions. Laser ablation as a full-face resurfacing procedure has also been shown to prevent the appearance of new NMSCs [1, 17].

Pulsed-dye lasers (PDL) and Nd:YAG lasers that target the vasculature have been also used for the treatment of superficial and nodular BCCs [18, 19]. In a study by Jalian et al., 75 % of tumors less than 1 cm in diameter responded to combined treatment with both lasers [18]. In a study by Ortiz et al., the Nd:YAG laser was used for the treatment of BCCs on the trunk and extremities on lesions with a diameter less than 1.5 cm and achieved clearance rates of >90 % proven by histopathology [19].

Chemical Peels

Not only has chemical peeling proven its efficacy in improving photodamaged skin, but a few studies have also shown satisfactory effects in the treatment of AKs (Fig. 3) [1, 20, 21]. Chemical peeling involves the controlled application to the skin of one or more exfoliating agents, resulting in different levels of peeling (superficial, medium depth, deep) depending on the agents used and techniques followed.

Advantages of using chemical peeling in the treatment of AKs include, in addition to the reduction in the number of lesions, the diffuse nature of the treatment and the added skin rejuvenation effect [1, 20]. In fact, one study showed that

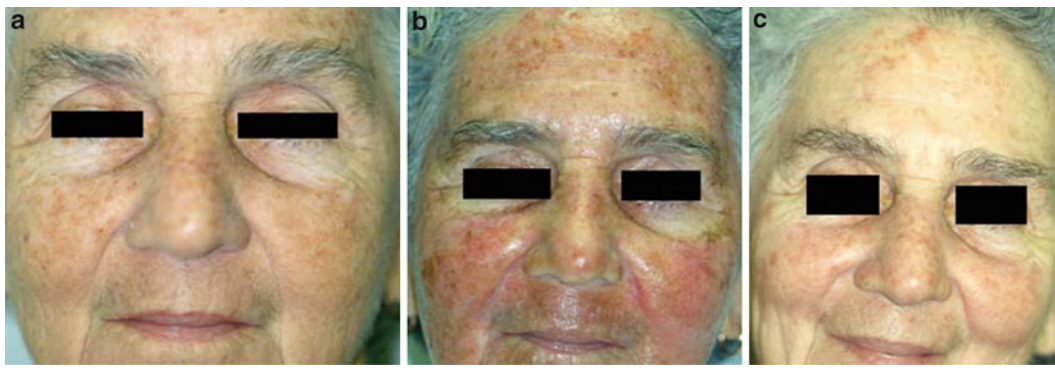

Fig. 3 Elderly woman with extensive AKs over the face treated with chemical peeling: (**a**) before treatment, (**b**) during treatment, and (**c**) after treatment

medium-depth peeling (Jessner's solution followed by 35 % trichloroacetic acid) was as effective as 5 % 5-FU cream applied twice daily for 3 weeks. In another study, Kaminaka et al., used 100 % phenol on 46 patients with AKs and Bowen's disease with 84.8 % clearance response after a 1-year follow-up [22].

Disadvantages of chemical peeling include prolonged healing time and the self-pay nature of the procedure. Adverse effects depend on the depth of injury reached by the chemical peel and include persistent erythema, secondary infection, dyspigmentation, and scarring, as well as cardiac, renal, and hepatic toxicity (associated with deep phenol peels) [1, 20, 21].

Dietary and Herbal Effects

Recently, there has been great interest in the presumed benefits provided by dietary modifications and herbal supplements in the prevention or even treatment of cutaneous malignancies [3]. Extensive work has been done, with only a few studies showing significant benefit. In one study, a low-fat diet was associated with significantly lower incidence of actinic keratosis development compared to a high-fat diet. However, more recent larger RCT studies have shown no association between low-fat diets and prevention of NMSCs [23]. Other studies on animal models have shown that the polyphenols from black and green tea may inhibit UV-induced photocarcinogenesis. In addition, more recent studies suggest a benefit for prevention of NMSCs with resveratrol (found in grapes, red wines, berries, and peanuts) and lycopene (found in red fruits and vegetables) [23].

Conclusion

Elderly people constitute a special, expanding patient population that is more prone to develop cutaneous malignancies. Although surgery is usually considered the first-line management option for the treatment of cutaneous malignancies, elderly patients are, not uncommonly, found to be poor surgical candidates because of multiple causes, including age and associated medical comorbidities, among others. In such cases, alternative modalities of treatment may be of great benefit. The unique properties of the different modalities should be known, as well as the characteristics of the tumor (size, type, and location) and the patient profile, in order to choose the best modality to treat our patients. In the future, more randomized controlled trials are needed in order to reach standard guidelines for the use of these different modalities and also to test new therapies that are continuously emerging.

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