Lasers in skin cancer prophylaxis

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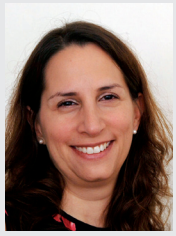

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"...the laser technologies, which have undergone incremental improvements in tolerability and sophistication to expand their use in medical and aesthetic dermatology, will find increasing use in treating photoaged skin for prophylactic purposes."

Skin cancer is the most common malignancy, with over 1 million cases diagnosed annually in the USA, comprising more than a third of cancers in the USA [101]. Cutaneous malignancies are amenable to early diagnosis and treatment, owing to their visual accessibility; the same advantage should facilitate preventative measures in high-risk individuals or in cases of known or suspected premalignant lesions. Topical and systemic pharmaceuticals are used in daily practice, but lasers – which have hitherto been limited to the treatment of diagnosed malignancies – provide a safe and well-controlled technology for treating focal or wide areas at high risk for cutaneous malignancy. The lasers used act by a variety of mechanisms, including selective photothermolysis, nonselective ablation or through the use of coherent light sources for photodynamic therapy. These mechanisms and the ability to apply them directly make lasers a promising tool in the dermatologist's armamentarium in the battle against skin cancer.

Current state of skin cancer & its prophylaxis

Non-melanoma skin cancers (NMSCs), primarily basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) are a worldwide epidemic. One in five Americans will be diagnosed with NMSC in their lifetime, at a total direct cost of care exceeding US$1 billion [1,102]. BCC, the least malignant of the NMSCs, develops on skin that is chronically sun exposed and account for 75–80% of NMSCs. Nearly 20% of NMSCs are SCCs, which also arise in skin that is chronically sun-exposed, particularly the face, scalp, ears, lips, dorsal arms and hands. SCCs can be aggressive if diagnosed at later invasive stages. Ideally, SCC is diagnosed in its 'precancerous stage' as an actinic keratosis (AK), although AK is increasingly accepted as SCC *in situ*, with estimates of transformation to full-thickness epidermal SCC ranging from 0.25 to 16% [2]. The remaining NMSC include vascular tumors (e.g., Kaposi sarcoma), cutaneous T-cell lymphoma, Merkel cell carcinoma and rare sarcomas (e.g., angiosarcoma and dermatofibrosarcoma protuberans). These, as well as melanoma, will not be addressed in this article.

Prophylaxis in high-risk individuals

The most effective and safest approach for skin cancer prophylaxis is, of course, strict sun avoidance and the use of sunblock. However, the bulk of patients who are in need of prophylactic approaches for skin cancer have already absorbed sun-induced mutations and actinic damage. In these patients, specific remedies must be chosen based on the individual need and ability to comply with treatment.

The risk of NMSC is increased by history of significant sun exposure as well as by the medical context. Individuals with genetic predisposition owing to skin phenotype (light skin or red/blonde hair) or familial skin cancer predisposition (basal cell nevus syndrome, epidermodysplasia verruciformis, or Muir–Torre syndrome) should be screened annually or more often for new or suspicious lesions. Patients with known photosensitivity disorders, such as albinism or xeroderma pigmentosum, have a lifetime risk of NMSC approaching 100% and require extremely close monitoring. Patients with immune deficiencies, such as those induced by hematological malignancy, use of immunosuppressive drugs, or AIDS, are also at increased risk because of

EXPERT REVIEWS

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diminished immune surveillance. These populations will benefit from a proactive approach in addition to monitoring. Furthermore, the presence of AK in any individual is a marker for the high risk of developing NMSC, both in the area of the visible AK and on other body sites. This observation is in keeping with the concept of 'field cancerization', which poses that the skin around an identified malignant or premalignant lesion harbors precancerous cells or mutations [3–5]. These patients are particularly suited to prophylactic treatment of the high-risk areas.

Current approaches to skin cancer prevention

Topical imiquimod 5%, an immune response modifier, was initially US FDA approved for the treatment of condyloma, and was subsequently studied for the treatment of AK, Bowen's disease (SCC in situ) and superficial BCC [6,7]. Imiquimod stimulates a local immune response, in part via Toll-like receptors and increased local levels of various chemokines, along with a putative direct antineoplastic effects on tumor cells [8–10]. The major benefit of topical imiquimod is its therapeutic effect on field cancerization. The same benefit has been harnessed for prophylaxis in high-risk individuals, in whom areas heavily affected by AK are treated with imiquimod for a period of 16 weeks. The use of imiquimod is limited at times by its severe erythema and eczematization of the treated skin, which lasts for the 16 weeks of treatment. The use of imiquimod has overtaken the previously common use of topical 5-fluorouracil 5% cream, which was selectively taken up by proliferating cells and exerted a local chemotherapeutic effect.

> "Given the rapid evolution of therapeutic strategies for NMSC that are safe and well tolerated, there is a reduced barrier for applying these technologies for prophylaxis in high-risk patients."

Photodynamic therapy (PDT) is based on an oxygen-dependent reaction between a photosensitizing molecule and light, wherein a photosensitive prodrug is activated by light into a cytotoxic molecule. The prodrugs may be endogenous molecules, such as porphyrins, or exogenous drugs such as 5-aminolevulinic acid (5-ALA) or the methyl ester of ALA (mALA). The main activating light sources are red light (640 nm) and blue light (400–450 nm). Topical ALA preferentially accumulates in rapidly proliferating cells, including premaligmant and malignant cells, where it is converted into protoporphyrin IX (PpIX); upon light exposure, PpIX generates reactive oxygen species that have a local cytotoxic effect. As with imiquimod, this modality allows treatment of both visible precancerous or cancerous lesions, as well as 'prophylaxis' in the adjacent skin. The major advantage of PDT over imiquimod is its short treatment time.

Retinoids are known to induce normal differentiation of cell lines and to inhibit the growth of malignant cell lines [11]. They are effective in prophylaxis, particular of AK and SCC, and their use either locally or systemically is a valuable approach in reducing the risk of NMSC in very high-risk populations, such as organ transplant recipients [12]. However, their topical use and, more markedly, their systemic use is limited by side effects and they are not suitable for use in pregnancy. Other pharmacologic approaches include topical NSAIDs and chemical peels [13–20].

Spectrum of lasers & their role in cancer therapy & prevention

Lasers may be used in skin cancer prophylaxis based on specific effects on certain cells, by their nonspecific ablation of the epidermis, or by their use as coherent light sources in PDT. Each approach enables the use of specific lasers.

Ablative approaches

The most nonspecific approach involves elimination of the premalignant cells in the cancerization field. This can be achieved by any destructive modality, including chemical peels or ablative lasers. Studies have focused on CO_2 lasers and Erbium:YAG lasers.

Ablation with CO_2 laser (10,600 nm) achieves a depth of 150–200 µm in a single pass, which is adequate for coagulation of the superficial epidermis and elimination of squamous cells at risk for evolution to AK or SCC; there is some debate as to its ability to coagulate the basal cell layer if applied as a single pass, and it may hence be only partially effective in eliminating cells *en route* to BCC. Clinical studies corroborate this and suggest the need for deeper treatment, as can be achieved by multiple passes or modifications of the protocol. In an early study, 14 patients with diffuse facial AK underwent CO_2 laser resurfacing with significant long-term reduction in AK burden [21]. Soon thereafter, Massey *et al.* reported two patients with histories of multiple facial NMSCs (including one patient with 25 prior BCCs) who were treated with two-pass CO_2 laser resurfacing [22]. No new NMSC developed in the treated area at 33 and 52 months, despite new lesions outside the treated area. In a larger study, 35 patients with Fitzpatrick I–II skin underwent CO_2 resurfacing [23]. Five (14%) developed AK or BCC in treatment field within less than 1 year. This study prompted discussion regarding the depth of ablation needed, and led to a published opinion that multiple passes, performed to a deeper depth and with greater control than afforded by chemical peels, should provide superior results [24].

Similar results were reported from two retrospective studies. Iyer *et al.* analyzed 24 patients with Fitzpatrick skin type I–II, with at least 5 years history of AK and more than 30 facial AK at the time of treatment [25]. At follow-up 1 or more years after a single facial resurfacing treatment with CO_2 and/or Erbium:YAG, 87% were AK free for at least 1 year and 58% were AK free for 2 years. In addition, four BCCs or SCCs developed in this group, of which, two were within the first year. Ostertag performed a similar retrospective case–control study of 25 patients treated for widespread AK, with a mean follow-up of 39 months (range 7–70 months) and found 44% of patients to be recurrence free [26].

Hantash *et al.* performed a randomized, prospective, case–controlled 5-year trial involving 34 patients, assessing the effect of resurfacing for treatment of AK and prevention of BCC or SCC [19]. Patients were randomized to one of three treatment arms: CO_2, trichloroacetic acid peel 30% or fluorouracil

cream 5% applied twice daily for 3 weeks. Treated patients were compared with the control patients. All three treatment arms were effective, reducing AK count by 83–92% ($p \leq 0.03$) and reducing the incidence of NMSC compared with the control group ($p < 0.001$), with a trend toward longer time to new BCC/SCC ($p = 0.07$). Of note, no significant differences were noted among the treatment groups.

Actinic cheilitis, a premalignant condition of the lips, is associated with significant risk of progression to SCC. Orenstein *et al.* treated 12 patients with actinic cheilitis with Erbium:YAG laser [27]. No recurrences were observed within the follow-up time (8–36 months, mean 23 months).

> "Combination modalities and fractional ablative lasers … are current areas of study; the evidence from these studies will be key indicators in guiding the trend from topical to laser-mediated prophylactic strategies."

In recent years, the approach to ablative resurfacing has changed with the advent of fractional resurfacing [28]. In this approach, a matrix of small, closely spaced beams are delivered at very high energies, to generate focal ablation to the dermis, with intact intervening epidermis. The benefit of the approach is twofold: the retained epidermis allows faster healing, as re-epithelialization need only develop within small distances between the ablated columns and the tolerated energy within the ablated columns can be much higher. The approach has proven effective in the treatment of photoaging, with fractionated CO_2, 2940 nm Erbium:YAG, 1550-nm diode-pumped erbium, and combined 1320-/1440-nm lasers [29–47]. While this approach does not eliminate confluent layers of precancerous cells in the epidermis, repeated passes and treatments should significantly reduce occurrence of AK, BCC and SCC in high-risk patients, and its improved tolerability will make it an option for individuals unable or unwilling to tolerate the significant downtime and risks associated with full resurfacing.

Two studies have been published to date addressing the use of fractional lasers in actinic damage. Lapidoth *et al.* treated 28 patients with mild-to-moderate actinic damage with fractional Erbium:YAG laser, applying one-to-four treatments at 4-week intervals [31]. Clinical assessment 2 months after the last treatment showed excellent results in 75% of patients, and good results in 25%. Further follow-up at 6–9 months showed maintained effects. Chrastil *et al.* have also shown a benefit in the treatment of disseminated superficial actinic porokeratosis, an actinic condition associated with increased NMSC risk, with fractional ablation [48].

Laser PDT in skin cancer prophylaxis

As mentioned, PDT is used for the treatment of NMSC and large areas of actinic damage, and is amenable to use as a preventative approach. The light can be applied in a noncoherent manner or by laser. Therapeutic use of the pulsed dye laser (PDL) with PDT has been shown to be effective in treating AK, BCC and SCC *in situ* [49–51]. In these indications, the mechanism is a direct cytotoxic effect on cells due to preferential absorption of topical ALA by rapidly dividing cells. It appears that PDT stimulates immunomodulatory effects as well. It is not yet the standard of care to treat all BCC and SCC with PDT, but the modality is appropriate for patients who cannot undergo definitive treatment (Mohs or standard excision) owing to medical reasons or cosmesis, and whose lesions are thin enough to allow complete treatment. However, the modality is ideally suited to prophylaxis, given its tolerability, nonscarring nature and benefit in the cancerization field.

Photodynamic therapy can be delivered with lasers or incoherent light sources. Incoherent light sources have the benefit of lower cost and greater treatment area, as well as proven efficacy [52]. Red lasers, in particular the PDL, are used in PDT because of their greater skin penetration than blue light, despite slightly lower absorption by porphyrins. Furthermore, PDL has been used with an improved side-effect profile and shorter light-exposure time [53,54]. It is possible that PDL may offer an additional benefit due its independent coagulation of vasculature and the focal hyperthermia generated [55].

Actinic cheilitis is particularly well-suited for PDL-PDT because of the focal nature of the light exposure. Alexiades-Armenakas and Geronemus examined the effect of long-pulsed PDL with topical 20% 5-ALA in 19 patients [56]. After one-to-three treatments at 1-month intervals, 68% had complete clearance after a mean of 1.8 treatments (37% after one, 11% after two and 21% after three treatments). At a mean follow-up of 4.1 months (range 1–12), one patient (5%) showed recurrence.

Future directions

Ruiz-Rodriguez *et al.* provide a novel approach to treating photoaged skin, in a pilot study combining fractional resurfacing and PDT [57]. After two sessions of fractional resurfacing of the perioral area using 1550 nm, half the area was treated with methyl 5-aminolevulinate. Visual assessment after complete healing revealed increased improvement in superficial wrinkles in three out of the four patients on the combined-treatment side. Such an approach may be well suited for prophylactic treatment. It is critical that the PDT be performed immediately after the fractional resurfacing, so that the uptake of ALA by proliferating cells does not interfere with wound healing. An additional benefit is increased penetration of the ALA in the perforated skin after fractional resurfacing; while this undoes some of the benefit of the preferential uptake of ALA by cancerous or precancerous cells, the deeper penetration and diffusion may increase the efficacy. Patients in the Ruiz-Rodriguez study tolerated the procedure well.

Another approach that may be of value is a two-step process, whereby fractional resurfacing is followed 2 weeks later by imiquimod. Not only does the combination provide a more aggressive overall approach, but the imiquimod can destroy any premalignant cells that remain after fractional ablative resurfacing.

Other approaches that may maximize the effects of two modalities might include short-course treatment with imiquimod, followed by PDL. Imiquimod 'highlights' the precancerous lesions with erythema, which will render these lesions obvious and an improved target for PDL.

Given the rapid evolution of therapeutic strategies for NMSC that are safe and well tolerated, there is a reduced barrier for applying these technologies for prophylaxis in high-risk patients. Individuals with a personal history of NMSC or AK, or who have clinical contexts that place them at high risk of developing NMSC (e.g., immunosuppressed states, genetic predisposition and severe sun damage) will increasingly be managed proactively, and regular examinations will be supplemented by topical and procedural interventions to reduce the risk of NMSC. In parallel, the laser technologies, which have undergone incremental improvements in tolerability and sophistication to expand their use in medical and aesthetic dermatology, will find increasing use in treating photoaged skin for prophylactic purposes. Combination modalities and fractional ablative lasers, which have only begun their application in this arena, are current areas of study; the evidence from these studies will be key indicators in guiding the trend from topical to laser-mediated prophylactic strategies.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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