Australasian Society of Cosmetic Dermatologists

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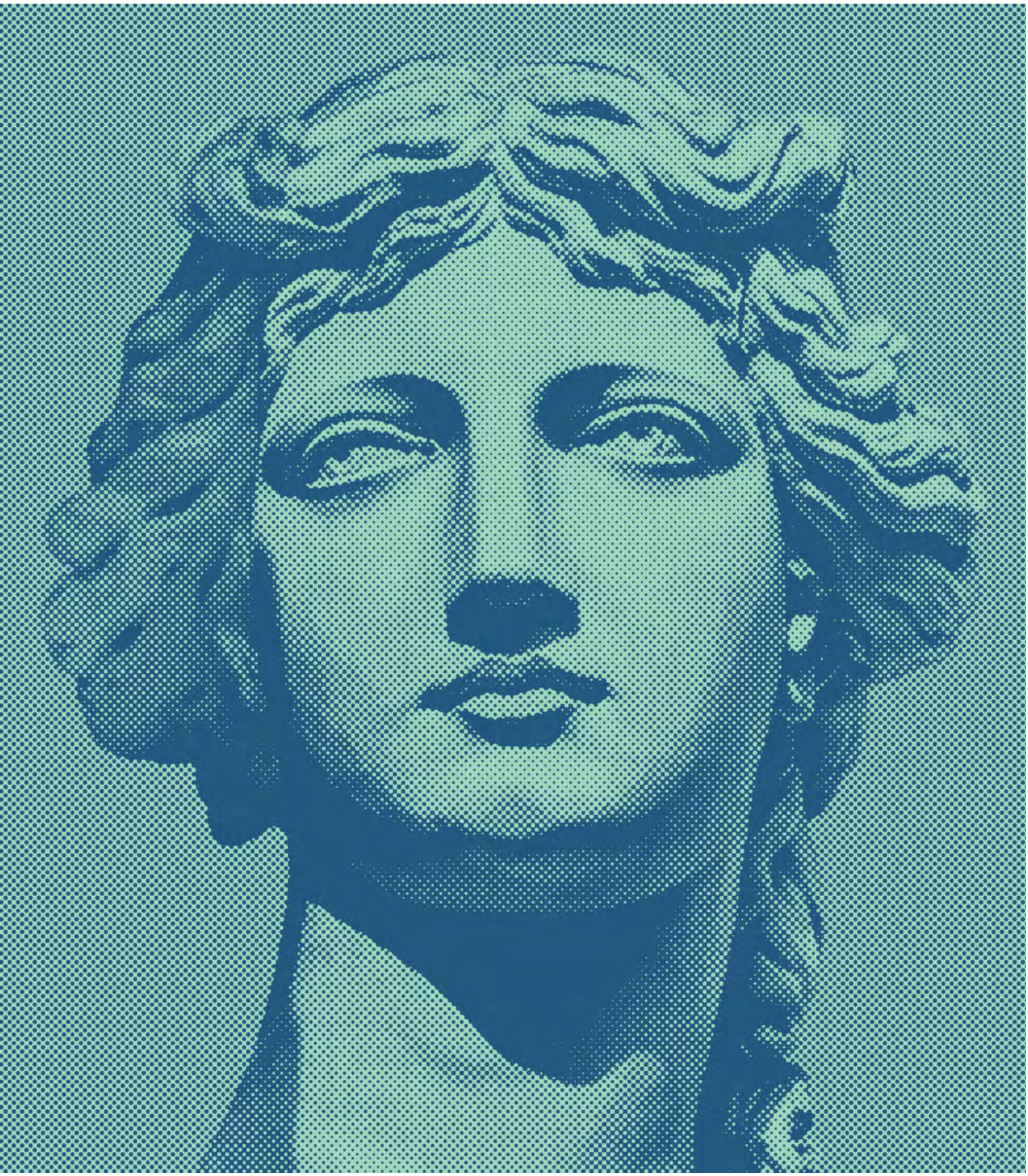

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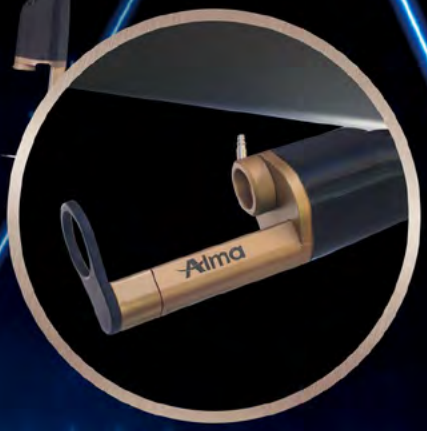

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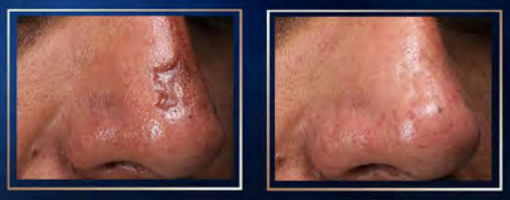

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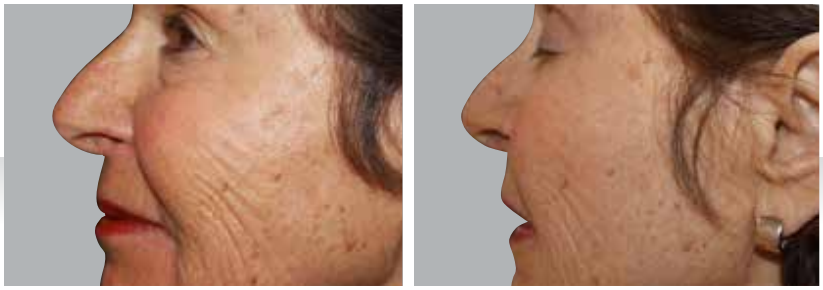

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Reference 1. Hema Sundaram, MD, Vivian Bucay, MD, & Monika Kiripolsky, MD 'Skin Aging & Photo Damage Improvement Using a DNA Repair and Anti-Glycation Skin Care Regime'. Made in the U.S.A.

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OPINIONS AND PROGRESS IN
Cosmetic Dermatology
VOLUME 01 / ISSUE 03 / NOVEMBER 2021

Welcome to **"Photodamage 1" – the first of a two-part series on sun damage, skin cancers and photoaging.**

We are delighted to have Associate Professor Michael Freeman and Dr John Sullivan as guest editors for this issue. They have put together an excellent content covering key aspects of photodamage that will continue the OPCD aims of educating and informing our readers.

In this issue we are introducing the OPCD podcasts, hosted by Dr Davin Lim, to further explore topics of interest through a series of interviews with opinion leaders and experts.

The journal will now move to a triannual publication schedule: March, July and November issues. We are indeed fortunate to be able to call on local and international Dermatology colleagues for contributions. In particular, we are very grateful to be able to work with Australian Dermatologists and their Research Fellows to produce interesting and relevant content for the journal.

As we launch this issue, Melbourne and Sydney have celebrated their versions of "Freedom Day", followed by a graduated re-opening of international borders. We hope these are forward steps towards safe, celebratory and socially interactive COVID-normal times.

Off the back of the success of the first two issues of OPCD, we appreciate any feedback to help us to continue to improve on future editions and meet your education needs.

Co-Editors in Chief
Dr Adrian Lim
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Contents

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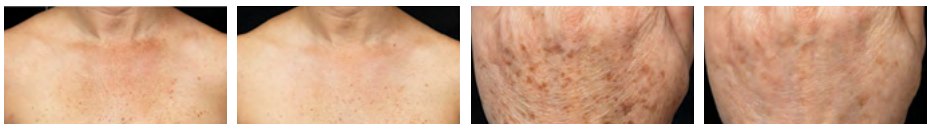

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Photodamage 1 Guest Editorial

Guest Editors: Michael Freeman[1,2] and John R Sullivan[3,4,5]

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Freeman M, Sullivan JR. Photodamage 1. Guest Editorial. Opin Prog Cosmet Dermatol 2021;1(3):1.

This edition of the journal is the first of two parts on photodamage. It is well recognised that chronic exposure to sunlight is the most significant extrinsic risk factor for photoaging, poor cosmesis and benign and malignant skin lesions. Patients and clinicians alike spend a significant amount of time and resources in preventing and treating the consequences of photodamage. In this issue, readers will rediscover the biologic mechanisms of photo damage and photoaging together with prevention and the treatment of its dysplastic consequences.

Saxon Smith discusses the historical perspective of ageing from the pock marked face of Queen Elizabeth I of England to the realities of self-criticism of facial features with Zoom conferences. In Prudence Gramp's article, you will be reminded that 80% of ageing signs can be increased by photodamage and as much as 50% of the total sun exposure prior to the age of 60 occur before the age of 20.

The different wavelengths of UVA and UVB are discussed and while both are damaging to the skin, they can have different effects and because of this, preventative measures need to be considered. Prevention is paramount to reduce the effects of photodamage with sun-protection the most important measure. Sunscreens do not always provide equal protection against different wavelengths of light which is discussed by Joseph and colleagues in their article, which outlines the different sunscreen options. When selecting a sunscreen, we have a responsibility to consider that Hawaii has banned oxybenzone and octinoxate because of studies suggesting adverse effects on corals and other aquatic life.

Previously, the effects of visible light and infrared radiation were not given much consideration. While tanning beds are now out of fashion, consumers of saunas, that emit infrared light, may need to reconsider the risk of photodamage. Infrared remains a complex topic as it can be both beneficial and deleterious depending on breadth of wavelength and dosage.

Sarah Hanna et al. clarifies the different oral preventive therapies available for skin cancer chemoprevention. These are particularly important for sufferers of non-melanoma skin cancer (NMSC) in particular, where reductions in squamous cell carcinoma can be achieved with acitretin and nicotinamide by up to 30%. One would assume the finding of lower vitamin D levels found in cohorts of NMSC is due to the more extreme photoprotection that has been recommended. Oral antioxidants are covered and the protective evidence for leafy green vegetables.

This issue introduces some of the therapeutic measures that can tackle photodamage. Farrell and Shumack explore the non-surgical therapies for skin cancer including cryotherapy, 5-flurouracil and imiquimod, which are providing alternative options to patients other than the gold standard of surgical excision. John Sullivan expertly details the nuances of photodynamic therapy and the ability to increase absorption with fractionated CO2 laser and the various modalities to activate the protoporphyrin with not just LED lamps but IPL.

We hope this edition provides insight into the mechanisms of photodamage and introduces you to the preventative and treatment options available, which will be explored further in part two. It is an exciting time to be in clinical dermatology as we have a new understanding of the complexity of the science behind photodamage and the different effects of radiation types on the skin. We look forward to watching future research and ongoing evaluation of the multitude of treatments to broaden our understanding of photodamage and we hope this aids you to provide better outcomes for your patients.

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Photodamage and Photoaging: Epidemiology and Pathogenesis

CLICK IMAGE TO LINK TO VIDEO DURATION_01:07

Prudence Gramp[1], Michael Freeman[1,2]

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Disclosures: *none*

OUTLINE: Photoaging is a type of extrinsic ageing caused by chronic exposure of the skin to sunlight (photodamage). Many of the signs of chronological ageing are shared with photoaging however it is now clear that 80% of ageing signs can be increased by photodamage. Increased radiation exposure can result from outdoor lifestyle choices such as in Australia where most of the population resides on the coastlines and the warm climate promotes outdoor living with a high ultraviolet (UV) index for much of the year. The most significant cause of photoaging is chronic, repeated exposure to UV radiation. UVB is recognised to be the major risk factor for the majority of skin cancers and UVA is the major risk factor for photoaging. UV radiation has been shown to cause mitochondrial DNA alterations and epigenetic changes within skin. The production of reactive oxygen species can cause collagen degradation and remodelling and an increase in proinflammatory cytokines which leads to many of the visual effects of photoaging. The visual changes of photoaging manifest as fine and coarse wrinkles, telangiectasias, pigment changes, as well as a loss of tone, translucency, and elasticity. Chronic exposure to sunlight also increases the risk of benign and malignant skin lesions such as lentigines, senile purpura, actinic keratoses, basal cell carcinoma, squamous cell carcinoma and melanomas. Infrared radiation has a variable impact on the skin with small doses causing skin rejuvenation and a photoprotective effect, however large doses can increase photoaging by acting on fibroblasts and degrading collagen and elasticity. This new understanding of the contributing factors of photoaging will assist in prevention and treatment and will also prompt new areas for research.

KEYWORDS: photodamage, photoaging, skin ageing, epidemiology, pathogenesis, UV radiation

Gramp P, Freeman M. Photodamage and Photoaging: Epidemiology and Pathogenesis. Opin Prog Cosmet Dermatol 2021;1(3):3-8.

Introduction

Photoaging is a type of extrinsic ageing caused by chronic exposure of the skin to sunlight (photodamage). The visual changes of photoaging manifest as fine and coarse wrinkles, telangiectasias, pigment changes as well as a loss of tone, translucency, and elasticity. Chronic exposure to sunlight also increases the risk of benign and malignant skin lesions such as lentigines, senile purpura, actinic keratoses, basal cell carcinoma, squamous cell carcinoma and melanomas which are cosmetically undesirable and can be life threatening.

Ageing of the skin has been shown to be influenced by many factors including genetics, pollution, smoking, heavy alcohol use and chronic poor nutrition.[1] However, ultraviolet (UV) radiation and infrared radiation are the most significant causes of photoaging and have been shown to cause mitochondrial DNA alterations and epigenetic changes within skin. The production of reactive oxygen species can cause collagen degradation and remodelling and an increase in proinflammatory cytokines which leads to many of the visual effects of photoaging. Risk of photodamage and subsequent photoaging is increased with older age, male sex, fair skin (skin types I to III) and chronic and prolonged sun exposure over a lifetime.[1,2] Increased sun exposure can be a result of residing in cities with high radiation levels as well as occupational and recreational activities that include outdoor exposure.[1] The tendency to live on the coastlines and adopt outdoor lifestyles contributes significantly to increased photoaging in the Australian population.

Epidemiology

Genetics and skin type are strong risk factors for photoaging, however cumulative sun exposure remains the most damaging. Sun exposure can occur from outdoor recreational activities or occupational exposure, however the amount of sun exposure in

childhood years (often with direct links to location of residence) has been demonstrated to have a strong influence in photodamage risk later in life.

It is estimated that around 50% of the total sun exposure prior to the age of 60 occurs before the age of 20 with young people spending more time in the sun than adults.[3] Photoaging, melanocytic naevi and melanoma rates are higher in Australian compared with British children, which is thought to be due to increased time spent outdoors.[3] It is estimated that children of Australia, Europe, Japan, Mexico, UK and USA spent an average of between 1.5 to 5.1 hours outdoors per day between 1990 and 2005.[3] Studies among Queensland school children showed an average of 1.7 to 3.0 daily hours in the sun, with 3.2 to 4.1 hours in some parts of Queensland such as Nambour.[3,4] Male sex has also been recognised as a risk factor which is supported by a Queensland study showing boys spent 28% more time in the sun than girls.[3]

After adjusting for confounding factors such as skin type and age, severity of photoaging has been linked with high rates of sun exposure as well as multiple episodes (>10) of sunburning.[5] Damage to the skin in childhood may not be seen for many years but after the age of 30 there is a rapid advance in photoaging signs with an estimated 14% risk of more severe photoaging signs for every year of age after 30.[3]

Ethnicity influences type and extent of photoaging with multiple studies showing that while Asian women develop wrinkles at a later age than European women with the same sun exposure, they exhibit an earlier onset of pigmentation changes.[6,7]

UV radiation varies depending on the time of day and latitude of location as the UV index is greater in the middle of the day and increases depending on the proximity to the equator. Australia has one of the highest levels of UV radiation with Queensland, Northern Territory and Western Australia having an average annual noon-clear sky UV index of between 8 and 14 (very high to extreme).[8] UV radiation is also at its worst when there are reflective surfaces such as snow and sand.[8] The UV index is typically at its highest between 11am and 1pm (12pm and 2pm daylight savings time), and sun protection is recommended whenever the intensity exceeds a rating of 3.[8] In Australia the UV index is highest in January with an average of 11 in the whole of Australia and lowest in June and July where it can vary widely depending on location with an average of 2 in Tasmania and 9 in far northern Australia.[8] The regions in the world with the highest UV index are those that lie closest to the equator including many South American countries such as Peru, Chile and Argentina.[9]

Signs and assessment of photoaging

Diagnosis and assessment of severity of photoaging can be evaluated with histological analysis that shows dermal elastosis: a pathological degenerative change which occurs from increased elastin accumulation and collagen breakdown.[2,10] There can also be epidermal atrophy and a thinning of the spinous layer.[1]

A less invasive and more common method to evaluate extent of photoaging is through clinical examination and photomapping of visual signs.[11] A French study from 2013 developed standardised photographic scales to allow for objective evaluation of photoaging signs on the face.[12] The Glogau photo-damage/wrinkle classification scale is a simplified scale to help clinicians quickly identify levels of skin ageing (see figure 1).[13]

Figure 1. *Glogau Photoaging and Wrinkle Classification Scale*[13]

Type I	Mild	Expected age 28-35 years	No wrinkles	Early photoaging, minimal wrinkles, mild pigment changes, no keratoses
Type II	Moderate	Expected age 35-50 years	Wrinkles in motion	Early-moderate photoaging, wrinkles induced by movement, some pigmentation changes, mild skin texture changes, early actinic keratoses
Type III	Advanced	Expected age 50-65 years	Wrinkles at rest	Advanced photoaging, wrinkles present at rest, prominent pigmentation changes, telangiectasias, actinic keratoses
Type IV	Severe	Expected age 65-70 years +	Only wrinkles	Severe photoaging, widespread wrinkles, yellow/grey skin discolouration, pigmentation changes, actinic keratoses +/- cancerous lesions

Skin type influences the extent and type of photoaging signs. Fine lines (rhytides) are more commonly found with Fitzpatrick skin types I and II while deep wrinkles are more common in skin types III and IV.[2] In Caucasian people photoaging can also be classified as hypertrophic (more likely in type III or IV) and atrophic (more likely in type I and II) (see Figure 2).[14]

Figure 2. *Hypertrophic and atrophic photoaging skin types*[14]

Photoaging signs	Hypertrophic	Atrophic
Pigmentation	Dyschromia	Focal hypopigmentation
Texture	Leathery	Smooth
Wrinkles	Coarse wrinkles	Minimal or fine lines
Vascular	Minimal changes	Telangiectasia
Dysplastic	Minimal changes	Common: Solar keratoses, BCC, SCC
Fitzpatrick Skin Type	Type III or IV	Type I or II

While there are many signs of skin ageing it has been estimated that 80% of visual skin ageing signs are attributable to or increased with UV exposure (see Figure 3).[12] A study which evaluated 298 Caucasian women with a standardised visual scale implemented by 12 dermatologists found that increased pigmentation was more prominent with greater sun exposure, demonstrating a statistically significant risk.[12] Pigmentation changes can include hyperpigmentation, hypopigmentation, dyschromia and melasma. Photodamage has also been shown to cause solar lentigos due to an increase in melanocytes and production of melanin in sun exposed areas, especially on the dorsum of the hands or the face.[15]

It has been demonstrated that changes in skin texture and an increase in wrinkles are associated with both increased sun exposure and chronological ageing.[12] The extracellular matrix of the dermis consists of elastic fibres and collagens (mostly type I and III) which give it strength and provides structure. The loss of parts of this extracellular matrix, most prominently collagen, leads to wrinkling of the skin. Photoaging causes an increase in both fine and course wrinkles as well as making the microrelief more pronounced, giving the skin a leathery feel.[2,12]

Vascular changes such as telangiectasia are a common skin ageing sign but the cause is multifactorial including smoking and photodamage. Chronic photodamage has been shown to disrupt normal vasculature of the skin and show an increase in telangiectasias.[16,17]

Dermatoporosis is a process that leads to chronic cutaneous insufficiency and its causes are multifactorial with photoaging being a contributor. Patients with dermatoporosis have very fragile skin and suffer from senile purpura, stellate pseudoscars and wound healing issues.[14]

Figure 3. *Photoaging signs*[12]

Pigmentation	Hyperpigmentation • Whole face pigmentation however most pronounced in the lower part of the face, the outer lateral maxilla and the malar area Melasma • UV exposure contributes to the development of melasma with an increase in melanin deposition Dyschromia • Uneven patches of skin colour of hyper or hypopigmentation including guttate hypomelanosis • Most pronounced in the lower third of the face
Wrinkles	Fine and coarse wrinkles Upper lip – vertical lines Lower lip – from corner of lower lip, directing towards the chin Cheeks – course wrinkles with random direction, no connection with lines of muscular structure Jawline – course wrinkles/folds extending from subauricular along the lines of the neck
Solar Elastosis	Thickening, yellowing, coarsely wrinkled skin due to increased deposition of elastin
Texture	Deposition of elastin and breakdown of collagen can be perceived as coarseness or fine nodularity Upper-lip – thickened, accentuated microrelief Cheeks – dryness or leathery texture Chin – thickened or dimpled appearance, accentuated microrelief
Vascular	Telangiectasias (broken capillaries) – small linear red blood vessels
Dermatoporosis	Chronic cutaneous insufficiency/atrophy Fragile skin, senile purpura, stellate pseudoscars, wound healing issues

Pathophysiology

Ultraviolet radiation

UV radiation from sunlight is comprised of UVA (320-400 nm), UVB (280-320 nm), and UVC (200-290 nm). UVC, which is highly damaging to skin does not reach the earth's surface as it is absorbed by ozone and moisture.[18] Of the UV radiation that does reach the skin, 95% is UVA while 5% is UVB.[18] UVB, due to its short wavelength, is absorbed in the epidermis and can cause sunburn, immunosuppression and is carcinogenic. UVA has a longer wavelength and is able to penetrate to the dermis. UVA radiation can cause tanning abd sunburn and has recently been recognised as a major cause of photodamage and photoaging.[19] UVA is not blocked by glass or clouds and has less variability throughout daylight hours.[17] UVB is considered to be the main cause of the majority of skin cancers and UVA is understood to have a significant role in both photoaging and the formation of some skin cancers.[17] Sunbeds for artificial tanning exposes users to large amounts of UVA as well as UVB and have not only been shown to increase risk of skin cancer but are also implicated in pre-mature photoaging.[20]

Cumulative UV radiation causes photoaging by direct cellular damage and production of reactive oxygen species.[18] Chromophores absorb UV radiation in the skin and include melanins, DNA, urocanic acid and amino acids.[21] When UV radiation is absorbed, reactive oxygen species including singlet oxygen are produced which causes a cascade of events involving alteration of mitochondrial DNA in fibroblasts and keratinocytes, and an increase in the action of matrix metalloproteinase (MMP).[18,22,23] This unregulated increase in MMP causes destruction of collagen types I and III, a reduction in skin elasticity and a resultant increase in wrinkling of the skin.[22,23]

DNA also suffers from direct effects when it absorbs UVB photons. This causes nucleotide rearrangements which activates the nucleotide excision repair pathway.[19] Some people have a deficiency in the 9 major proteins in this pathway and incomplete repair leads to cellular dysfunction and increased photoaging.[19] It has recently also been demonstrated in mouse models that UV radiation can shorten telomeres that cap chromosomes in stem cells in the skin.[24] Shortening of telomeres leads to cell senescence (cell cycle arrest and dysfunction) and apoptosis (cell death) which gives weight to the theory that UV radiation causes photoaging through stem cell depletion.[19,24]

UV radiation has been linked with pigmentation disorders such as melasma through direct and indirect processes that cause an increase in melanin. Visible light upregulates opsin 3 which causes an increase in melanin stimulating hormone receptor activity in the epidermis resulting in greater melanin deposition.[25,26] This is consistent with clinical findings which find that pigmentation disorders have the highest correlation with heavy sun exposure.[12]

Vascular changes have also been recognised as a sign of photoaging. Acute exposures to UV radiation and infrared cause an increase in vascular endothelial growth factor which promotes skin angiogenesis.[27] These newly formed blood vessels are immature however and have increased permeability leading to increased inflammation. Over time this increased inflammation is thought to be a contributor to the decreased dermal vasculature in chronically photoaged skin and chronically damaged skin is also associated with the development of telangiectasias.[17,27]

Infrared radiation

Until recently, most photoaging was considered attributable to UV radiation. It has been suggested that chronic low-dose exposure to longer wavelengths such as infrared radiation may contribute to the age-related volume changes in the face.[28] Severe skin aging may develop on those exposed to chronic infrared sources due to professions such as on bakers' arms because of exposure to hot ovens and on the faces of glass blowers.[29]

Recent research is looking into the effects of infrared radiation (also known as thermal radiation) and visible light in photoaging. Kim et al. showed that chronic repetitive exposure to heat via infrared radiation also leads to skin wrinkling in mice.[30] The fluence was far higher than natural irradiance; the dose was the equivalent to 3½ hours of natural infrared radiation exposure 5 days a week for 15 weeks.

Infrared radiation comes from both natural sources such as sunlight (of the solar energy that reaches the skin infrared A, B, and C make up about 40% of it and about 40% of that represents IR-A) and fire, and artificial sources such as heaters, tanning beds, lamps and saunas.[31] Visible light comprises 39% of solar energy that reaches the skin. Due to the longer wavelengths in infrared radiation (760 nm-1 mm) and visible light (400-760 nm) there is deeper penetration into the skin layers, reaching to the deep dermis and subcutaneous and affecting cells involved in the extracellular matrix of the skin such as fibroblasts.[22] The effects of infrared radiation in the skin can be both beneficial and deleterious depending on breadth of wavelength and dosage.

Controlled exposure to low intensity infrared radiation (also known as photobiomodulation) has been used to improve wound healing and tissue regeneration, to treat pain and stiffness of rheumatoid arthritis, and to encourage neural stimulation.[32] It is believed that this controlled level of near infrared bands promotes tissue changes due to the light exposure, without the thermal

effects.[32] It has been demonstrated in acute controlled exposure that infrared radiation stimulates collagen production and improves elasticity in the skin.[33] A sub-division of infrared radiation (far infrared radiation, FIR, 3-25 μm), has also been observed to stimulate cells and tissue in both in vitro and in vivo studies.[34] Moreover, FIR therapy is considered a promising treatment modality for insomnia and arthritis.[35]

Environmental infrared radiation which has a wider spectrum is now being heavily researched as it is implicated as a contributor to skin ageing. Infrared radiation causes production of reactive oxygen species which, in small amounts, has a rejuvenating effect and some protective effects against UV radiation damage.[32] However larger amounts and chronic exposure to reactive oxygen species can be degenerative to the skin.[32] Similar to UV radiation, chronic infrared radiation increases MMP which results in a reduction in collagen types I and III and further reduction in skin elasticity.[22,23] The direct contribution of heat energy from infrared further increases MMP but also promotes angiogenesis resulting in chronic vascular changes.[23] Long term exposure to environmental infrared radiation is now being considered a likely contributor to photoaging. It appears that lower irradiance (< 50 mW/cm^2 - approximately half of the sun's mid-day fluence) is less likely to induce skin hyperthermia which would otherwise lead to potential deleterious effects.[36] Thus avoidance of prolonged middle of the day exposures would seem prudent.

Epigenetic changes

Recent studies have been exploring the possibility that UV radiation can cause epigenetic changes in epithelial cells which are permanent, heritable alterations to the genetic material. With the differentiation of cells, DNA methylation is a requirement for the many different functions of cells in the skin. Methylation of DNA causes an alteration of gene expression and can change the function of the cell, often by suppression. A recent systematic review by de Oliveira and colleagues found that UV radiation can cause hypermethylation of some of the tumour suppressor genes (such as *p16* and *RASSF1*) and hypomethylation of oncogenes (such as **WNT1**).[37] This resulted in a decrease in tumour suppression gene activity and an increase in oncogene expression, which overall increases the risk of malignancy.[37] Some of the studies in this review demonstrated that individuals who had a disruption of the DNA methylation homeostasis in the epidermis and dermis also had a concurrent increase in photoaging signs. Others, however, did not demonstrate evidence that global methylation was disrupted with UV radiation.[37] Because light is used as a therapy in dermatology and is needed for vitamin D production, further research in epigenetic changes would be of benefit.

Conclusion

Recent research has led to a greater understanding of the risks and causes associated with photoaging. Multiple contributing factors have been identified within the literature. Chronic repeated exposure to UV light and infrared A radiation causes photodamage over a lifetime that leads to photoaging. Photoaging results in distinct changes in the skin including wrinkling, pigmentation, vascular and texture changes, and loss of tone and elasticity. Many of the signs of chronological ageing are shared with photoaging however it is now clear that 80% of ageing signs can be increased by photodamage. UV radiation leads to direct DNA damage and the loss of extracellular matrix, most prominently collagen types I and III, which leads to wrinkling of the skin. Photodamage causes significant pigment changes in the skin due to an increased deposition of melanin. Epigenetic changes have been demonstrated with increased UV radiation exposure, however the implication of this is difficult to ascertain. Infrared A radiation has a variable impact on the skin with small doses causing skin rejuvenation and a photoprotective effect, however large doses can increase photoaging by acting on fibroblasts and degrading collagen and elasticity. UVB is recognised to be the major risk factor for the majority of skin cancers and UVA is the major risk factor for photoaging, although they both contribute to either effect. This new understanding of the contributing factors of photoaging will assist in prevention and treatment and will also prompt new areas for research.

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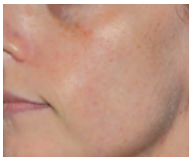	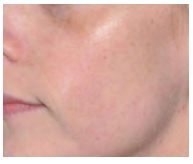
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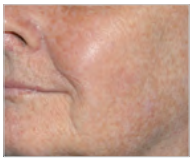	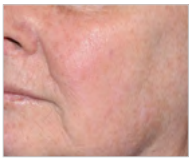
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A Historical Perspective on the Evolution of Ageing

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Photoageing and antiageing is big business in 2021. There are topical therapies, oral therapies, and device-based therapies to attempt to prevent or repair the damage that ultraviolet rays (UVR) have on our skin throughout our lifetime. However, the focus on the role of UVR in ageing of the skin is a relatively new concept in recent decades and associated with an accelerated consciousness in the age of 'The Selfie'.

For centuries, there was a classist distinction by the complexion of one's face. The aristocracy and the wealthy class strived for a porcelain appearance to their skin and differentiation from the sun beaten, outdoor-working lower classes. The skin of the upper classes was not necessarily naturally a smooth milky complexion but rather more often achieved through the thick application of lead-based foundation. In fact, Queen Elizabeth I of England had very pockmarked skin and was famous for her religious application of "Venetian ceruse", a mixture of vinegar and lead. However, this pursuit of long-term beauty was the cosmetic's use of white lead as its base pigment, potentially leading to poisoning, damaging the skin, causing hair loss, and if used over an extended period could cause death.[1]

By the 1800s in Europe and the UK, there had been a move away from makeup and a 'naturally' clear complexion became the ideal. Young upper-class women were directed to stay out of the sun as a way by which to encourage a porcelain skin.[2] They might bathe a few times a month to encourage a natural light rouge tinge to their cheeks. On the other hand, makeup was still an expensive option for the lower classes who would make do with red tissue paper, extracting the red dye to lightly apply to their cheeks.[2]

With the advent of the industrial age, the classes and distribution of wealth shifted, with the middle classes thriving. This resulted in larger populations having access to disposable incomes as well as technology bringing down the price of cosmetics; affording people to holiday, often by the seaside. This saw a dramatic shift away from the 'peaches and cream' complexion as the sign of social stature, towards a 'healthy tanned' skin indicating the ability and financial means to holiday and pursue idle outdoor activities.

In the 1960s, especially in countries like Australia and New Zealand, idle play and outdoor activities were commonplace. The clothing worn to pursue these activities covered less and less skin, exemplified by the advent of bikinis and Speedo briefs. Tanning had become largely a national occupation with a plethora of commercial brands and homemade concoctions to promote the tanning process.

However, the relationship between UVR exposure and skin cancer risk gradually became part of the social vernacular with the introduction of public health campaigns advocating the need to 'slip, slop, slap' in the 1980s. As an adjunct to this, individuals were becoming more concerned with the appearance of their skin as they aged and sought more therapeutic options to remedy the impact of photoageing on their skin. Although the use of sunscreens when outdoors remained ado and family dependent.

By the late 2000s it had been well established that UV exposure is likely to contribute up to 80% of visible signs of ageing in the skin including wrinkling.[3] Antiageing products and treatments had become more affordable and accessible with the role of retinoids and retinols becoming popular to help repair photodamaged skin.[4]

Currently, we live in the age of digital cameras in everyone's pocket; accompanied by the belief that an event never happened unless a selfie was taken and uploaded to one's various social media platforms. However, the raw selfie itself is rarely enough unless it has had numerous filters to 'perfect' the image. Now, this has been further exacerbated by COVID-19 leading to Zoom meetings being the norm. This has made us even more aware of perceived imperfections as we regularly see ourselves in the 'gallery' of Zoom attendees.

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Photoaging and Sunscreens

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OUTLINE: Aging is an inevitable part of life and the skin is not spared in this process; however, premature skin aging is an undesirable, preventable, and treatable condition. Sun exposure leads to the most significant premature aging of the skin, known as photoaging, and will be the focus of this review. Although traditionally ultraviolet (UV) light has been implicated in most of the deleterious effects of sunlight, including photoaging, visible light and infrared light also have a role to play.

UV radiation, visible light and infrared radiation have been shown to cause photoaging through mechanisms involving the generation of reactive oxygen species (ROS), inflammatory pathway activation and matrix metalloproteinase (MMP) activation which lead to collagen degradation and abnormal elastin deposition. Sunscreens provide adequate protection against UVB light with broad-spectrum sunscreens providing UVA protection. There are limited options for the protection against visible light and infrared radiation and studies have focused on additives such as iron oxide and antioxidants for each condition, respectively.

Photoaging exacerbates the natural aging process and leads to unattractive skin changes such as deep wrinkles, thickened skin, roughness and pigmentation abnormalities. Employing a sun smart routine is essential to prevent this. This involves seeking shade when outdoors, wearing protective clothing, hats, sunglasses and most importantly, the application of a broad-spectrum high sun protection factor (SPF) sunscreen. Visible light and infrared radiation also have a role and strategies to protect against their effects are in infancy. Further research is important to provide a reliable answer regarding their efficacy and methods to demonstrate this.

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Introduction

Aging is an inevitable part of life and the skin is not spared in this process; however, premature skin aging is an undesirable, preventable, and treatable condition. The causes of skin aging are broadly split into intrinsic and extrinsic aetiologies. Intrinsic causes are difficult to prevent; they are genetically determined and represent the degradation process of the entire body.[1] Extrinsic causes are where prevention and treatment have a critical role and include smoking, diet, stress, sleep, environmental pollution and most importantly, sun exposure. Sun exposure leads to the most significant premature aging of the skin, known as photoaging, and will be the focus of this review. Almost all parts of the electromagnetic spectrum have been implicated in photoaging including ultraviolet (UV)B, UVA, visible light and infrared radiation (Table 1).[2] Preventing photoaging is anchored on the use of sunscreens and sun avoidance by either remaining under cover, indoors or using hats and garments that cover most of the skin. This type of advice is often poorly received, especially in a country like Australia, where there is a culture of deliberate tanning and sun exposure despite well-known risks of skin cancer and photoaging.[3] This review aims to summarise current knowledge of photoageing, the use of sunscreens and future trends in this field.

Photoageing

Photoageing refers to the phenotypic changes in skin that occur in addition to the effects of intrinsic chronological ageing. Intrinsic aged skin leads to atrophy, fine wrinkling and dryness; this is compared to the photoaged skin which has deeper wrinkling,

a thickened epidermis, laxity, dullness, roughness and pigment abnormalities.[4] Sunlight is the primary extrinsic factor that can expedite the molecular changes that lead to skin ageing and each part of the electromagnetic spectrum has a role to play in this process.[2]

UV radiation

UV radiation comprises of UVC (100-290nm) which has the highest energy but is absorbed by the atmosphere; UVB (290-320nm) and UVA (320-400nm), which is further split into UVA2 (320-340nm) and UVA1 (340-400nm). UV radiation poses a significant health burden as it is a primary cause of DNA damage that leads to cell death, photoageing and oncogenesis.[2] UVB forms the minority of UV light that reaches the skin (5%) and penetrates into the upper dermis contributing mostly to oncogenesis whereas UVA is the majority (95%), penetrates deeper into the dermis and exerts a more potent photoageing effect.[5] Mechanisms of UV induced photoageing include increased expression of matrix metalloproteinases (MMPs) including collagenase (MMP-1), gelatinase (MMP-9) and stromelysin (MMP-3). These are zinc-dependent endopeptidases that degrade skin collagen and lead to impaired structural integrity and accumulation of abnormal elastic fibres in the dermal connective tissue.[6] Moreover, UV light is absorbed by chromophores in the skin cells which generate reactive oxygen species (ROS) that have multiple effects. ROS are volatile and unstable molecules that need to oxidise nearby molecules to become stable. In the absence of endogenous antioxidants, ROS may directly damage lipids, amino acids, and DNA. The proposed mechanism in the context of UV-induced photoageing is the release of proinflammatory cytokines and activation protein-1 (AP-1) and nuclear factor-κB (NF-κB) which up-regulate key MMPs.[7] Furthermore, UV-induced ROS have been shown to decrease transforming growth factor–β expression, which decreases collagen production and enhances elastin production, contributing to photoageing.[8] ROS may also activate enzymatic and non-enzymatic cellular responses, and interfere with gene expression.[9]

Visible light

Visible light exists between the electromagnetic wavelengths of 400-700nm. It comprises 40% of solar radiation that reaches the earth and can lead to dermatological issues such as solar urticaria, photoallergic skin reactions, porphyrias and pigmentation issues.[10] Visible light, especially at the higher energy blue spectrum, has been shown to induce oxidative damage in vitro[11] leading to the production of ROS and MMP-1 activation.[2] These damage the collagen and lead to the deposition of disorganised elastin that causes the clinical phenotype of photoaged skin. Melanin pigment protects darker-skinned individuals (Fitzpatrick IV or more) against the effect of UV radiation, however, it has been shown that visible light may have more of an effect in these individuals due to increased absorption in melanin pigment of cells.[12] Visible light does not directly damage the DNA and has not been shown to increase the levels of inflammatory cytokines that UV does;[13] moreover, the levels of ROS that form are far lower when compared to UV radiation, especially in lighter-skinned individuals (Fitzpatrick type II or less).[14] Although its effect is not as potent as UV, it is still worth considering the role of visible light in photoageing, especially in darker-skinned patients.

Infrared light

Infrared radiation (IR) occurs at the electromagnetic wavelengths between 700nm to 1mm and is further divided into IR-A (700-1400nm), IR-B (1400-3000nm) and IR-C (3000nm-1mm). It accounts for half of the radiation that reaches the earth and shorter wavelengths can penetrate deep into the skin; IR-A can infiltrate as deep as the subcutaneous tissue and 65% reaches the dermis[15] whereas IR-C is absorbed in the epidermis and increases its temperature.[16] IR-A is a potent regulator of gene expression in skin cells and has been shown to be involved in photoageing by eliciting a molecular response similar to UV radiation.[16] The mechanism, however, is different with the formation of mitochondrial ROS in skin fibroblasts that lead to increased membrane permeability, apoptotic pathway activation and MMP-1 activation, which as a whole lead to dermal collagen breakdown and abnormal elastin deposition.[15] IR-A radiation has also been shown to cause cutaneous neoangiogenesis which is a prominent feature of photoaged human skin.[17] Finally, despite its potential harmful effects, IR-A has been successfully used therapeutically to treat sclerotic skin lesions or stimulate wound healing and further research into its therapeutic properties is important, much like the therapeutic properties of UV radiation in inflammatory dermatoses.[18]

Sunscreens

Since complete avoidance of the sun is not a practical approach, sunscreens are a critical measure in the prevention of photoageing and have the additional benefits of preventing sunburns, reducing mutagenesis and preventing skin cancer. The main protection conferred by sunscreens is towards UVA and UVB and there are limited mainstream options for the damage caused by visible light and IR-A radiation.

UV protection

Good UV protection requires uniform protection across the UVA and UVB range, an SPF and cosmetic elegance which will enhance compliance.[19] It is important to have uniform protection across the UV range because even though UVB rays are higher energy, cause more erythema and may induce more DNA damage, the absolute amount of UVA that reaches the skin is much higher and therefore substantially contributes to

the deleterious effects of UV radiation overall.[19] UV protection in sunscreens is conferred by UV filters which must be efficacious (absorb UV light within the range of 290-400nm), safe and registered. These filters include inorganic particulate materials such as titanium dioxide and zinc oxide which absorb UV energy through their semiconducting properties.[19] They also include organic particulate UV filters which absorb energy through electrons in their aromatic rings, a process which is described in detail by Herzog.[20] The UV filters used in Australian sunscreens are summarised in Table 2. The SPF is a measure of sunscreen protection against the effects of UVB – it measures the time taken until the minimal erythemal dose (MED) of sunlight is reached on the skin and allows comparison between different products. Assuming the MED of skin phototype I is 10 minutes; it would take 20 minutes for erythema to occur if an SPF 2 sunscreen was used and over 8 hours if an SPF 50 sunscreen was used. This is assuming ideal conditions including application of $2mg/cm^2$ and disregards the effects of water, sweat and the varying intensity of UV light throughout the day. Finally, compliance is a requirement for any treatment to be effective and sunscreens are no exception; formulating sunscreens with good cosmetic profiles and pleasing properties enhances patient compliance and as a result, prevents UV damage including photoageing. Internationally, acceptable and pleasing properties of sunscreens may differ. Lotions and creams are popular worldwide and there is particular popularity of sprays in the European and American markets.[19]

Visible light protection

Current sunscreens have minimal protection against visible light induced ROS and photoageing; for this reason, research should focus on finding suitable alternatives.[18] There are limited studies on products to protect against visible light. One such study by Schalka et al. evaluated pigmented sunscreens to determine their solar visible light protection factor (PF-VIS) and pigment protection factor (PPF).[21] They found that products containing iron oxide in their formulation had greater photoprotective efficacy against visible light. Given there is an effect of visible light on photoageing, additional research would be beneficial in preventing this, especially in darker-skinned individuals.

Infrared protection

Photoprotection against infrared light can be provided by inorganic UV filters and antioxidants.[18] A small proof of principle study showed that a topical mixture containing vitamin C, vitamin E, ubiquinone and a grape-seed extract prevented IR-A induced MMP-1 mRNA expression in vivo in human skin.[22] This has led to an increase in sunscreen and daily skincare products which include antioxidant properties that may improve IR-A induced photoageing effects. The difficulty with regulating such products is the lack of an endpoint, such as erythema with UV protection, and therefore claims of effectiveness could be misleading.[18] Since IR-A penetrates deep into the dermis, systemic delivery of antioxidants via dermal vasculature through oral supplementation is also an option to consider. There are no major studies known to the authors that validate this strategy in IR-A radiation. Moreover, ROS are important in the homeostasis of human physiological systems, especially in the maintenance of cellular function and integrity. There exists a balance between adequate and excessive antioxidants and the effects on normal physiological function.[23] It is for this reason that the use of antioxidants at supraphysiological concentrations may adversely affect physiological antioxidative balance.[23] Therefore, oral antioxidants may better be used in situations in which there is an inability to neutralize, both by the ROS excess and by the decline of endogenous systems, such as in UV related photoageing. Moreover, exogenous antioxidants available on the market have varying scientific evidence on efficacy, prompting close scrutiny on which product to use.[23] Finally, inorganic UV filters have IR-A reflecting properties but face significant compliance issues due to their visibility after application.

Future trends

UV protection is established, effective, safe and comparable. Protection against visible light and IR-A requires further research for certain products to be routinely recommended. Antioxidants have been the focus of research when aiming to prevent damage related to IR-A and this is based on the pathophysiological mechanisms of increased ROS. Broad-spectrum sunscreens containing topical antioxidants could provide the best protection against UV and IR-A radiation and could be recommended. There is a paucity of data for oral antioxidant supplementation and this should be the focus of future research.

DNA repair enzymes, such as photolyase, have also been proposed as an additive to sunscreens to prevent oncogenesis and photoageing. These work by repairing cyclobutane dimers which form as a result of DNA irradiation and supplement the endogenous DNA repair mechanisms. As a result of this, studies have demonstrated reduced the number of actinic keratoses, non-melanoma skin cancers and photoageing and this has been reviewed by Leccia et al.[24]

There is also evidence that different skin types may have unique photoprotective properties as well as vulnerabilities. Therefore, there may be a role for individualised protective methods and sunscreen ingredients. For example, darker-skinned patients who should benefit much more from visible light protection can be offered sunscreens with ingredients that protect against this.

Conclusion

Photoageing exacerbates the natural ageing process and leads to unattractive skin changes such as deep wrinkles, thickened skin, roughness and pigmentation abnormalities. These changes have negative effects on the appearance, image and self-esteem of patients and methods of prevention are important to discuss. Completely avoiding sunlight is the ideal way to stop photoageing; however, it is not realistic and employing a sun smart routine is essential. This involves seeking shade when outdoors, wearing protective clothing, hats, sunglasses and most importantly, the application of a broad-spectrum high SPF sunscreen. Although it is UV radiation that classically has been attributed to the photoageing effect of sunlight, the role of the rest of the electromagnetic spectrum that reaches our skin has only recently been elucidated. Visible light and infrared radiation reach our skin in much higher proportions compared to UV light and strategies to protect against their effects are in infancy and include additives to sunscreens such as antioxidants and iron oxide. It remains to be seen whether these methods are truly effective and methods of studying their efficacy is difficult. Further research into topical and oral antioxidants is important to provide a reliable answer regarding their efficacy and methods to demonstrate this.

Table 1. *Radiation from sunlight, mechanism of photoageing and methods of protection*

Radiation	Wavelength	Penetration	Proposed mechanisms of photoageing	Protection
UVC	200-290nm	No skin penetration	Absorbed in the atmosphere	
UVB	290-320nm	Epidermal skin penetration	Damages DNA, generates ROS which activate inflammatory pathways, activates MMPs which degrade collagen	Sunscreens with UVB filters
UVA2	320-340nm	Dermal skin penetration		Sunscreens with UVA filters (broad-spectrum)
UVA1	340-400nm	Dermal skin penetration		
Visible light	400-700nm	Subdermal skin penetration	Generates ROS which active inflammatory pathways and activate MMP-1 production (much lesser extent than UV)	Sun avoidance, clothing, hats, iron oxide pigment sunscreen
IR-A	700-1400nm	Shorter wavelengths penetrate into subcutaneous skin	Generate ROS in fibroblast mitochondria leading to increased membrane permeability, apoptosis and MMP-1 activation. Also causes cutaneous neoangiogenesis	Sun avoidance, clothing, hats, antioxidant additive to sunscreen, oral antioxidant
IR-B	1400-3000nm	No skin penetration		
IR-C	3000nm-1mm	No skin penetration		

Table 2. *UV filters used in Australia (adapted from Osterwalder et al[19])*

Spectrum of protection	International nomenclature of cosmetic ingredients (INCI)	INCI abbreviation
Broad-spectrum including 340-400nm — UVA1	Bis-ethylhexyloxyphenol methoxyphenyl triazine	BEMT
	Butyl methoxydibenzoylmethane	BMBM
	Diethylamino hydroxybenzoyl hexyl benzoate	DHHB
	Disodium phenyl dibenzimidazole tetrasulfonate	DPDT
	Drometrizole trisiloxane	DTS
	Menthyl anthranilate	MA
	Methylene bis–benzotriazolyl tetramethylbutylphenol	MBBT
	Terephthalylidene dicamphor sulfonic acid	TDSA
	Zinc oxide	ZnO
Protection against 290-320 nm — UVB — UVA2	4-Methylbenzylidene camphor	MBC
	Benzophenone-3	BP3
	Benzophenone-4	BP4
	Polysilicone-15	PS15
	Diethylhexyl butamido triazone	DBT
	Ethylhexyl dimethyl PABA	EHDP
	Ethylhexyl methoxycinnamate	EHMC
	Ethylhexyl salicylate	EHS
	Ethylhexyl triazone	EHT
	Homomenthyl salicylate	HMS
	Isoamyl p-methoxycinnamate	IMC
	Octocrylene	OCR
	Phenylbenzimidazole sulfonic acid	PBSA
	Titanium dioxide	TiO2
	Tris biphenyl triazine	TBPT

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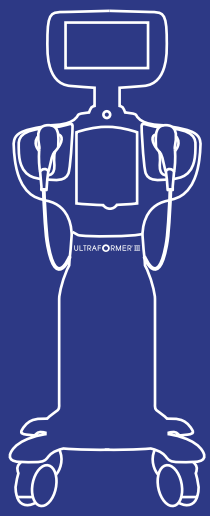

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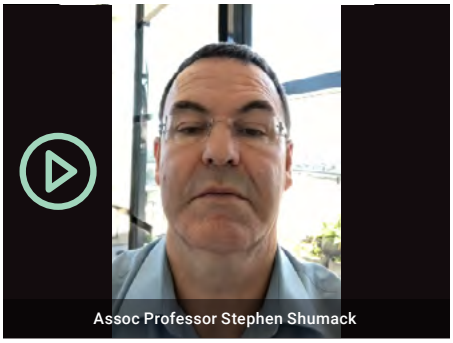

CLICK IMAGE TO LINK TO VIDEO DURATION_01:10

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OUTLINE: Skin cancers are exceedingly common, with keratinocyte (non-melanoma) skin cancers (KC) estimated to outnumber all other cancers combined. Surgical excision remains the "gold standard" as the only therapeutic option that not only provides histopathological diagnosis but also proof of margin control. However, due to patient preference, comorbidities, and tumour size and location, not all skin cancers are appropriate for surgical management. Fortunately, a number of topical therapies have been developed to assist with KC management. Cryotherapy with liquid nitrogen, 5-fluorouracil cream, imiquimod cream, photodynamic therapy, and radiotherapy are all widely used options with good efficacy rates. There are also newer oral therapies as a topic of emerging research.

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Introduction

Skin cancers constitute the largest number of cancers diagnosed in Australia each year.[1] Furthermore, Australia has the highest incidence of skin cancer in the world with 300 diagnoses per 100,000 population in 2018.[2] There has been an increasing incidence of both melanoma and keratinocyte (non-melanoma) skin cancers (KC), with KC estimated to outnumber all other cancers combined.[1] While surgical management remains the "gold standard" there is a great demand for alternative treatment options.

The commonest skin cancers are basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs), and melanomas. BCCs are the commonest skin cancer and arise from follicular stem cells in the epidermis. They arise from skin exposed to UV radiation, and thus have a high mutational burden.[3] BCCs cause significant morbidity through local tissue invasion and destruction. They have the very rare potential to metastasise although they rarely cause death. There are three main subtypes: superficial, nodular, and sclerosing. Superficial BCCs have a low risk of recurrence, however nodular, and in particular sclerosing, BCCs may recur more commonly. These subtypes are thus less suitable for topical therapy which does not have the same high efficacy rates as surgical excision.[4]

SCCs constitute 20% of keratinocyte cancers.[2] Up to 5% of patients will develop metastasis, with survival rates of 70% to 90% at 3-5 year follow up.[4] Pre-cancerous actinic keratoses arise from sun-damaged skin. Actinic keratoses in turn may uncommonly develop into SCC in situ or Bowen's Disease, and then invasive SCC. Exposure to ultraviolet light is the strongest risk factor for SCC development.[2]

Melanomas comprise less than 2% of skin cancers.[2] Queensland, Australia has the highest rate of melanoma globally, with 71 cases per 100,000 people between 2009-2013.[2] Melanomas range from lentigo maligna, or melanoma in situ, in the epidermis to more invasive disease. The gold standard of treatment is primary surgical excision with wide margins of 0.5-2 cm.[5] Due to the risk of metastatic disease, non-surgical treatment options are used far less frequently. However, for in situ disease there is a role for topical therapy where surgery is not desirable.

Surgical excision remains the gold standard for most skin cancers as it is the only treatment option that provides histopathological confirmation of diagnosis and clearance. However, the decision to operate is affected by considerations including patient comorbidities, tumour size, and location. Additionally, in cases where there are many clinical and subclinical

lesions over a large anatomical area, there is an obvious benefit from field therapy.

We discuss below the non-surgical therapies for skin cancers including cryotherapy, 5% fluorouracil, 5% imiquimod, photodynamic therapy (PDT), and radiotherapy. We will finish by touching on the emerging systemic agents.

Topical therapies

Cryotherapy

Cryotherapy with liquid nitrogen is the most common treatment for actinic keratoses in Australia.[6] It causes the formation of ice within the extracellular compartment, which then mechanically damages the cell membrane. Further, it induces vasoconstriction, endothelial damage and thus ischaemic necrosis of the tissue.[7] The intent is to affect a similar amount of tissue as would be removed with surgical excision. Cryotherapy has advantages in that it is simple and inexpensive.[4] Further, it is useful when treating patients with large numbers of lesions where other therapies may be impractical.

Cryotherapy can be used for well-demarcated superficial or nodular BCCs. It is contraindicated for ill-defined or sclerosing BCCs. The recommendation is to freeze the tumour and 5-10 mm of surrounding skin for 30 seconds. This is allowed to thaw for up to 5 minutes before being refrozen for another 30 seconds.[7] There is a cure rate of at least 95% with this method.[7,8] In general, cryotherapy is operator dependent, although the greater the size of the tumour, the lower the cure rate.[4] Typically, there tends to be slow healing over 1-2 months and a hypopigmented scar. It is thus a less suitable treatment option for cosmetically sensitive areas on the face or ears, or for lesions in pigmented skin.[4] Tumour location below the knee is a relative contraindication due to prolonged wound healing[6,8] and potential ulcer formation.

Although cryotherapy is commonly used to treat actinic keratoses, it does not have comparatively high success rates. A randomised study with one year follow up compared cryosurgery (20-40 seconds per lesion), 5-fluorouracil twice daily for four weeks, and imiquimod three times per week for four weeks.[9] Cryosurgery achieved 68% clinical clearance, 5-fluorouracil achieved 96% clinical clearance and imiquimod 85%. In comparison, sustained clinical clearance after 12 months was most optimal in the imiquimod group (73%) compared to 5-fluorouracil (54%) and cryotherapy (28%).[9] In general, response rates usually correlate with the duration of freeze time. However, cryotherapy does have the advantage of treating the patient in the clinic, rather than a 3- to 4-week treatment course.[4]

Cryotherapy can be used to treat Bowen's disease. However, less well-differentiated lesions, recurrent lesions, or lesions on the head and neck are better treated via an alternative method.[4] Cure rates of greater than 95% are quoted in the literature, even with a single freeze cycle of 30 seconds and a minimum of 3 mm margins.[4] As with cryotherapy for BCCs, there is slow healing for lesions larger than 20 mm diameter and lesions on the lower legs. Unlike with BCCs, larger lesions do not have a reduced response to treatment and they have the option of being treated with overlapping treatment fields.[4]

Cryotherapy is not currently recommended to treat lentigo maligna.[5] The main drawback to topical therapy for lentigo maligna is the lack of histopathological confirmation of adequate treatment. This appears to be an issue especially in cryotherapy, with recurrence rates of up to 40%.[10] Melanocytes are sensitive, however, to temperatures between -4 to -7°C. A depth of at least 3 mm must be achieved with cryotherapy in order to destroy atypical melanocytes that extend into hair follicles.[10] Two cycles of one minute freeze followed by 2 minutes thaw, with margins of 10 mm, has been shown to achieve disease-free outcome for a mean of 75.5 months in 18 patients.[10] Cryotherapy has also been studied as an adjunctive treatment in combination with imiquimod to increase local inflammation with variable results.[10]

5-Fluorouracil

5-Fluorouracil (5-FU) is approved only for actinic keratoses and Bowen's disease in Australia,[4] but elsewhere is commonly used to treat superficial BCCs.[2] 5-FU is a pyrimidine analogue that binds to thymidylate synthase through the co-factor 5,10-methylene tetrahydrofolate. This then inhibits thymidine synthesis and causes defects in DNA replication and hence apoptosis.[4] Local reactions are to be expected, and include localised pain, burning, crusting, erosions and hyperpigmentation. The lesions can develop secondary infections, including herpes simplex.[4]

5-FU was the first topical therapy registered by the US Food and Drug Administration (FDA) for the treatment of superficial BCC.[11] Although there are different formulations, the 5% formulation is the most widely used and approved internationally.[2] A large randomised controlled trial with 601 histopathologically confirmed superficial BCCs compared the use of 5-FU to PDT with methyl aminolevulinic acid (MAL), and topical imiquimod.[12] The PDT arm consisted of two sessions one week apart, the 5-FU arm of twice daily application for 4 weeks, and the imiquimod arm consisted of daily application for five days per week for 6 weeks. Patients clinically tumour free at 3 and 12 months follow up were 80.1% for 5-FU, 83.4% for imiquimod, and 72.8% for PDT.[12] 5-FU was found to be non-inferior to and imiquimod was

found to be superior to MAL PDT, with more severe side effects in the PDT group. A five year follow up on this study found that 70% of 5-FU, 80.5% of imiquimod, and 62.7% of PDT patients were tumour free.[13]

Surgical removal is the mainstay of treatment for other BCC subtypes. It is also the mainstay of treatment for SCCs. However, the precursor lesions of actinic keratosis and Bowen's disease are not infrequently treated with 5-FU. A randomised controlled trial of 932 patients found that 5-FU applied twice daily for 4 weeks lead to complete clearance of actinic keratoses in 38% of patients compared to 17% of patients in the control group.[14] 5-FU tends to only be used twice daily for 2 weeks on more sensitive areas such as the face.[4] This causes inflammation that takes 1-2 weeks to settle. For Bowen's disease, current recommendations are for twice daily treatment for 4-8 weeks.[4] This appears to provide roughly 90% cure, with a 70% 12-month complete response rate with good cosmesis.[4] There are further studies comparing surgical excision compared to 5-FU currently underway.

5-FU does not currently appear to have a role in lentigo maligna, although combination treatment with imiquimod has been explored with mixed results.[15]

Imiquimod

Imiquimod is a nucleoside analogue of the imidazoquinoline family based on an adenine derivative.[2] It acts as an agonist of toll-like receptors 7 and 8 on the surface of antigen presenting cells, leading to upregulation of immune antitumour responses.[4] Although originally approved for genital warts, it has since been approved for treatment of actinic keratosis on the face and scalp, and superficial BCCs where surgery is considered inappropriate.[2,4]

The recommended treatment regimen for primary superficial BCCs is application to the tumour with a 5 mm margin, 5 times per week for 6 weeks.[4,16] The patient should be followed up 3 months post therapy. A study comparing imiquimod for both superficial BCCs and nodular BCCs demonstrated 85.1% clearance at 3 years and 83.8% clearance at 5 years for superficial BCCs, in comparison to 81.8% clearance at 3 years and 81.1% clearance at 5 years for nodular BCCs.[17] However, since it is only currently approved for superficial BCCs, histological confirmation of diagnosis is required for Pharmaceutical Benefits Scheme (PBS) reimbursement. Imiquimod has very good cosmetic outcomes.[12] Unfortunately, it is not as effective as surgical excision with clear margins of 4 mm, which has 98% clearance at 3 years and 97.7% clearance at 5 years.[6]

Imiquimod is effective in the treatment of actinic keratoses. 5% imiquimod used three times per week for 16 weeks leads to complete clearance of actinic keratoses in 57.1% of patients compared to 2.2% of control patients.[18] Current guidelines suggest 3 non-consecutive days per week in 4-week cycles. This is continued until clearance is achieved for up to 16 weeks, although it usually requires two cycles.[4] Local reactions are very common, and include significant erythema, scabbing and crusting, itching and burning.[4] This reaction may vary between patients and even between lesions on the same patient. Secondary infections may occur. This may require a rest period to allow the inflammation to settle before recommencing treatment.[4] Alternatively, formulations of 2.5% and 3.75% imiquimod have fewer adverse reactions but may have greater recurrence of lesions.[19] 5% imiquimod has superior clinical and cosmetic outcomes compared to 5-FU: one randomised controlled trial reported complete field clearance of actinic keratosis of 73% with imiquimod at 12 months, compared to 54% complete clearance in the 5-FU group.[9]

Bowen's disease can be treated with daily application for a total of 16 weeks.[20] This may provide 73% clearance for greater than 9 months.[20] In practice, more common treatment regimens involve 3-5 applications per week for 4-6 weeks. Breaks between applications may be required to allow inflammation to settle in some patients.[4]

Melanoma *in situ* can be a difficult condition to treat because there is frequently subclinical extension of disease beyond what is clinically evident. This leads to incomplete clearance by surgical excision with 5 mm margins in 50% of cases.[21] There are ongoing clinical trials currently exploring the use of imiquimod for lentigo maligna but current evidence is suggestive of 75% clearance as monotherapy and 95% clearance as adjunctive therapy post primary surgical excision without clear margins.[2,22] This is inferior to the results achieved with radiotherapy, however there is potentially a role for imiquimod as a preferred topical therapy in more challenging lentigo maligna lesions in elderly patients who may be unable to attend radiotherapy sessions regularly. Oversight by experienced clinicians is required.

Photodynamic therapy

PDT involves topical administration of a photosensitising agent (such as 5-aminolevulinic acid [ALA]), followed by an incubation period, and then the administration of light to trigger the release of reactive oxygen species. These reactive oxygen species damage cell membranes and thus trigger cell death.[2] An alternative photosensitising agent is a methyl ester of ALA, MAL, which appears to have greater tissue penetration and thus can target deeper lesions.[2] PDT is currently approved to treat actinic keratoses, Bowen's disease, and superficial and thin nodular BCCs.[2,4]

A treatment session involves gentle debridement of the lesion, or debulking of a nodular BCC, before application of the photosensitising cream to a thickness of 1 mm with a 5 mm margin. This is covered with an occlusive dressing and left in place for 3 hours. The area is then cleaned and exposed to illumination for up to 9 minutes.[4] A variation of this, daylight PDT, has recently been approved for actinic keratoses.[4] The recommendation is for application of MAL before daylight exposure for 2 hours.

PDT for BCC is usually well-tolerated with some pain during the illumination phase followed by formation of erosions and then healing over several weeks.[16] Occasionally, the pain can be sufficient to require temporary suspension of illumination or injection of local anaesthetic.[4] It offers a good cosmetic outcome.[12,16] Superficial BCCs appear to be more responsive to PDT compared to other subtypes.[16] Cure rates range from 72% to 100%.[2,12] There is evidence however that there is less recurrence with a second session of PDT, with 91% clearance compared to 68% at follow up of 6 years.[16] ALA and MAL PDT seem to have comparable effectiveness for BCCs.[16] Thin, nodular BCCs can be treated via PDT so long as lesions deeper than 2 mm are first debulked via curette or shave excision.[4] This is to allow the treatment to reach the full depth of the lesion. Thin nodular BCCs may achieve a 5-year clearance rate of 76% with a good cosmetic outcome.[23] It is worth noting that previous PDT does not affect future surgical outcomes.

Actinic keratoses and Bowen's disease can also be treated with PDT. Actinic keratoses can be treated effectively by PDT as large surface areas can be treated concurrently. For actinic keratoses, the recommendation is for a single session of PDT with effects assessed at 3 months.[4] Residual lesions should be treated again at this stage. ALA/PDT and MAL/PDT have a similar response rate of 90% when two sessions are used.[4] Unfortunately, lesion recurrence is a significant issue with perhaps 20% recurrence of actinic keratoses. Similar results can be achieved with daylight PDT with a reduced side effect of pain due to the reduced intensity of light exposure.[4] Bowen's disease can be treated with PDT, with a recommendation for two sessions of treatment 1-4 weeks apart.[4] There appears to be clearance at 6 months of 89% for ALA/PDT and 78% for MAL/PDT.[24] Recurrence may be as low as 17% after 64 months.[4] PDT is well-suited to the treatment of slower healing sites such as the lower limb, with less risk of development of a non-healing ulcer or infection compared to more destructive or surgical therapies.[4]

ALA/PDT has not been shown to be useful for the treatment of melanoma due to inefficient penetration of ALA into the skin.[2] The main disadvantage for PDT is the specialised equipment and training required, with the exception of daylight PDT. It is therefore restricted to centres specialising in skin cancer management.

Radiotherapy

Radiotherapy is an effective treatment that can be used to achieve cure, as well as in an adjunctive role post-operatively. It has a place in treating recurrent and metastatic disease, as well as in palliative therapy. Radiotherapy achieves this by affecting DNA. Normal tissue cells can repair much of the radiotherapy damage to their DNA within 6 hours after a single treatment. However malignant cells have poor repair capacity and do not survive.[4,25] Thus when used properly, radiotherapy has the ability to eradicate cancer cells whilst sparing normal tissue.

There are different types of radiotherapy. Brachytherapy is a method in which isotopes are applied to the surface of the tumour or inserted into it. The isotopes can be covered by a casing, which determines the dose rate.[4] This method allows for a high dose between the isotope and the tumour with a rapid fall off to deeper, non-malignant tissue. Brachytherapy also conveniently allows for irregular and curved targets to be treated.[16] An alternative method is superficial x-ray therapy, which is appropriate for depths up to 5 mm.[4] For lesions deeper than 5 mm, options include orthovoltage radiotherapy, megavoltage electrons, or photons produced by a linear accelerator.[4] As with other treatments, the radiation field includes the lesion as well as a surrounding margin depending on the tumour type.

Radiotherapy has the advantage of conserving tissue.[25] It can thus achieve superior functional and cosmetic outcomes compared to surgery, especially for cancers of the lips, eyelid commissures and nasal ala.[4] The main disadvantage is the requirement for multiple treatments (fractionation). Small doses, or fractions, are given to avoid exceeding the repair capacity of normal tissue and thus only remove malignant cells.[4] Smaller doses require a greater number of treatments and so the patient must visit the radiotherapy facility more often. However, smaller doses correlate with improved function and cosmesis.[4]

A commonly quoted disadvantage of radiotherapy is in-field radiation-induced cancer. This risk is likely overstated and is in the order of a rate of 1 in 1000 every ten years.[25] The association of radiotherapy with poor cosmetic outcomes (hypopigmentation, cicatrisation, telangiectasia, in-field fibrosis) is likely due to historical observations that do not take into account recent advances in the field.[4,25] Due to these concerns, radiotherapy was traditionally considered only in patients over the age of 70. It has been argued that it should be considered in patients as young as 40.[25]

One consideration in radiotherapy-treated skin is the poor surgical healing often encountered should the patient require an excision. Dehiscence leading to radio-necrotic ulcers and fistulae can occur.[25] Radiotherapy can be considered to re-treat any recurrence at the margin of the initial lesion, but due to the risk of radio-necrotic ulcers and fistulae, is usually avoided to re-treat the centre of previous radiotherapy fields.[25]

There are few clinical trials examining radiotherapy and skin cancer. There is thus limited high-level evidence regarding optimal treatment duration and therapy.[4,16]

For BCCs, radiotherapy is not limited to certain histological subtypes.[4] Several studies have reported efficacy of up to 90% after 5 years of follow up.[4] Recurrence is likely slightly higher than compared to surgical excision alone. Radiotherapy usually achieves good cosmesis, although brachytherapy has the least impressive results among the different radiotherapy subtypes.[4] Follow up post radiotherapy should occur 4 months afterwards, as the acute radiation reaction resolves 4-6 weeks after finishing radiotherapy and occasionally complete resolution clinically of a BCC can take 4 months.[4]

Radiotherapy for actinic keratoses has typically been considered as a last-line treatment for a minority of patients who fail other therapies.[4] Recent advances in external beam radiotherapy compared to the traditional brachytherapy moulds seem to provide better treatment for convex areas of field cancerisation such as the scalp.[4] Radiotherapy has also been reported to be useful in periungual Bowen's disease.[4]

As noted above, lentigo maligna is a difficult condition to treat.[21] Radiotherapy appears to be the best of the topical therapies, as it can provide 95% clearance of lentigo maligna after 3 years.[21] This is superior to imiquimod. Superficial radiotherapy is thus currently recommended as a suitable alternative to surgical excision of lentigo maligna, or as adjuvant therapy post-surgery for larger lesions with inadequate margins.[5]

Systemic therapies

Metastatic KC is rare, with metastatic BCC less than 0.1% of all cases and metastatic SCC less than 5%.[4] Metastatic BCC may be treated via targeted therapy against the hedgehog signalling pathway, such as with vismodegib and sonidegib.[4] The high mutation burden of BCC lends itself to checkpoint immunotherapy. In SCC, conventional chemotherapy is typically used despite limited evidence. Similar to BCCs, there is increasing evidence of the efficacy of checkpoint inhibitor immunotherapy in SCCs.[4]

Immunotherapy for melanoma, in particular metastatic disease, has a growing evidence base. Currently, there are recommendations for an anti-PD-1 immunotherapy as first-line for patients with unresectable stage III/IV melanoma.[5] Melanoma with a positive mutation for V600 BRAF should have first-line treatment with a BRAF inhibitor combined with a MEK inhibitor.[5] There are currently no head-to-head trials comparing these two treatments. However, there is agreement that all patients with unresectable stage III/IV melanoma should have testing for the V600 BRAF mutation, and should be considered for clinical trials.[5]

Conclusion

Non-surgical therapies for skin cancers have a role in patients in whom the benefits of non-surgical therapy outweigh the reduced efficacy rates compared to surgical therapy. Tumour type and subtype also have great importance in determining appropriate treatment choice. Topical therapy is an attractive option as it may achieve improved cosmesis and can be used to treat a wider field. This has the benefit of treating a greater number of lesions, and may also improve diagnostic accuracy in clearing less significant lesions to reveal hidden tumours. However, no topical therapy has the same efficacy as surgical excision, with most recurrence occurring within the first three years.[4] Thus, close follow up is warranted in these patients for at least 3 years following treatment.

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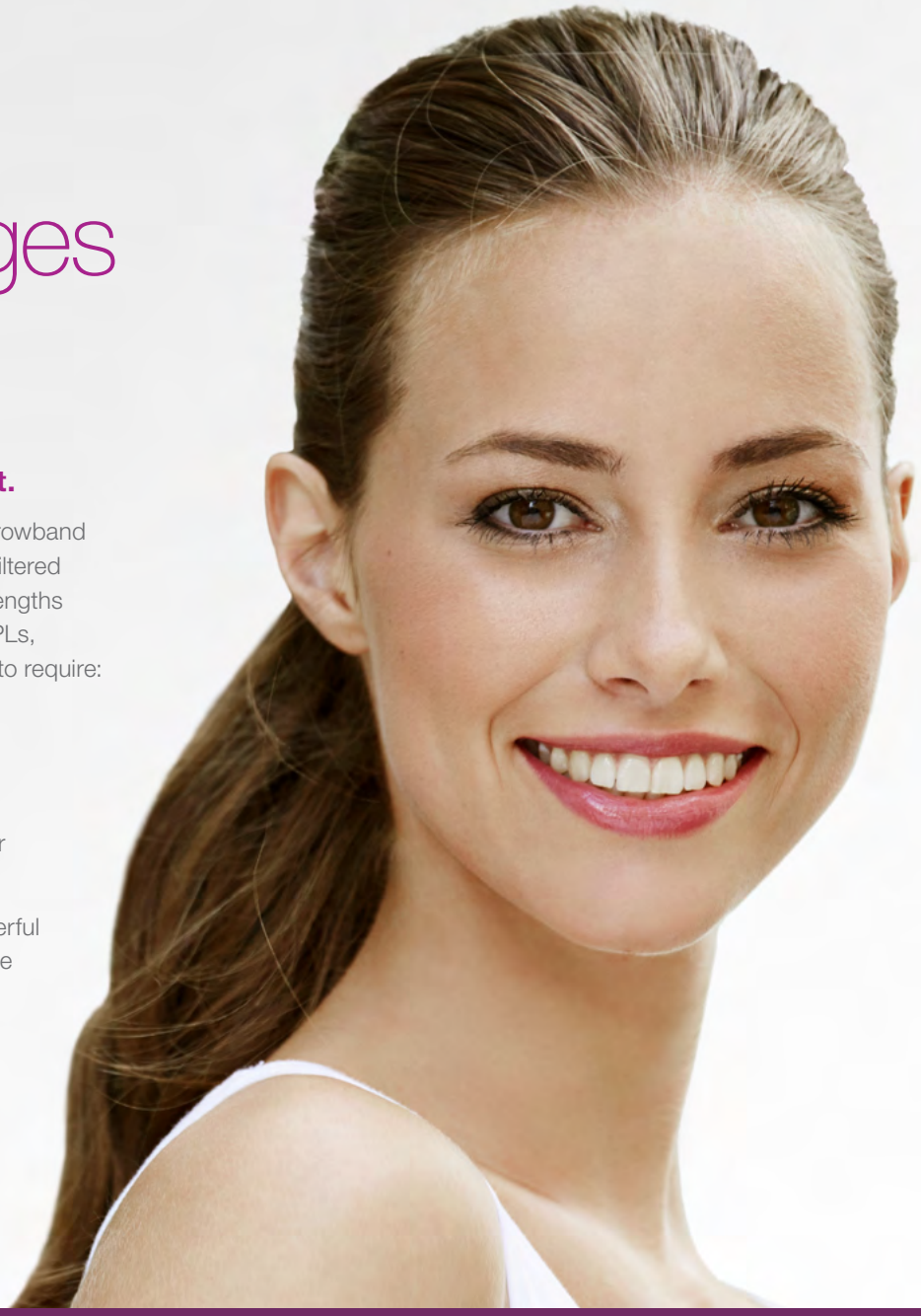

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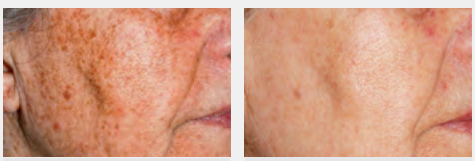

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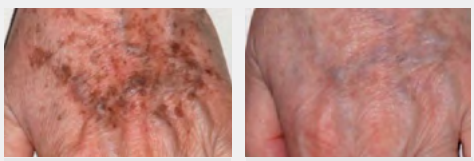

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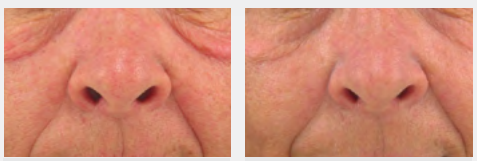

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Oral Preventive Therapies in Photodamaged Skin

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KEYWORDS: photodamage, prevention, non-melanoma skin cancer, photoprotection, chemoprevention

OUTLINE: Skin cancer risk increases with the level of ultraviolet radiation (UVR) exposure or photodamage. UVR is estimated to cause 65% of melanomas and 90% of non-melanoma skin cancers (NMSC). NMSC are the most common form of cancer diagnosis with significant morbidity for the patient and economic burden. In light of these factors, the prevention of NMSC is essential. Oral therapies for skin cancer chemoprevention include retinoids which are recommended for use in patients at high risk for developing multiple, invasive, or metastatic squamous cell carcinoma (SCC); nicotinamide which is well tolerated and has been shown to reduce actinic keratoses and SCCs; and non-steroidal anti-inflammatory drugs which may reduce SCC and basal cell carcinoma (BCC) but have well established side effects with prolonged use. Difluoromethylornithine has been shown to reduce BCCs but is limited by its side effect profile, including ototoxicity. There is evidence for using vitamin D, selenium, and plant-derived and animal-derived dietary products in the prevention of NMSC, but further studies are required to support their use and the required therapeutic regimen. Multiple novel agents are currently being investigated for NMSC prevention, including capecitabine, epidermal growth factor inhibitors, and synthetic alpha-melanocyte-stimulating hormones.

ABBREVIATIONS

5-FU:	Fluorouracil	NAD:	Nicotinamide adenine dinucleotide
AKs:	Actinic keratosis	NF-κB:	Nuclear factor-kappa B
ATP:	Adenosine triphosphate	NMSC:	Non-melanoma skin cancer
BCC:	Basal cell carcinoma	NO:	Nitric oxide
COX:	Cyclooxygenase	PARP-1:	Poly [ADP-ribose] polymerase 1
CPDs:	Cyclobutene pyrimidine dimers	PGE2:	Prostaglandin E2
DFMO:	Difluoromethylornithine	PL:	Polypodium leucotomos
DNA:	Deoxyribonucleic acid	ROS:	Reactive oxygen species
EGFR:	Epidermal growth factor receptor	RR:	Relative risk
ES:	Effect size	SCC:	Squamous cell carcinoma
HR:	Hazard ratio	UVR:	Ultraviolet radiation

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Introduction

The risk of skin cancer increases with the level of ultraviolet radiation (UVR) exposure or photodamage, especially with repeated UVR exposure with incidents of severe sunburn.[1] UVR causes an estimated 65% of melanomas and 90% of non-melanoma skin cancers (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[2]

The pathophysiological mechanisms by which UVR is implicated in the development of NMSC is complex. UVR can cause direct and indirect damage to deoxyribonucleic acid (DNA) and exerts an immunosuppressive effect that impedes the skin's ability to respond to developing NMSC.[3] Direct DNA damage occurs as photons of UVR are absorbed by chromophores in the skin, including DNA, melanin, amino acids, carotene and trans-urocanic acid.[4] DNA predominantly absorbs UVB radiation which causes photochemical reactions. UVR is also able to cause indirect damage to the DNA through the production of reactive oxygen species (ROS) and reactive nitrogen intermediates, which cause oxidative damage. The immunosuppressive effect of UVR is linked to the production of photolesions such as cyclobutene

pyrimidine dimers (CPDs)[5] and induction of other molecules with immunosuppressive properties such as interleukin-10, prostaglandins, platelet-activating factor and ROS.[6] UVR also results in changes to the skin's adaptive immune system by migration of Langerhans cells to draining lymph nodes[7], depletion of NAD and adenosine triphosphate (ATP) in the skin[8], inhibition of mast cells[9], cytotoxic T cells[10], and memory T cells.[11]

In 2002, NMSC was estimated to be the most common form of cancer diagnosed, with more NMSC diagnosed each year than all other cancers combined. From 2001 to 2016, the age-specific incidence rate of NMSC increased for people aged 50-59, 70-79, and 80 and over.[12] Although mortality due to NMSC is relatively low, with the age-standardised mortality rate for NMSC in 2016 estimated at 1.9 deaths per 100 000[12], the morbidity, such as disfigurement, is high. Further, NMSC is a significant economic burden with the cost of diagnosing and treating skin cancer in Australia in 2010 exceeding $536 million.[13]

In light of the significant morbidity and economic burden of NMSC, prevention is essential and a focus of current research. As the cause of most NMSC is known, it is largely preventable if suitable strategies can be developed. Primary prevention strategies are lacking, and given that the incidence of NMSC remains high, numerous systemic preventive methods have been explored over the past decades. Ultimately, the aim is to develop an oral photoprotective or chemopreventive agent that can be used in addition to primary prevention strategies.

Potential targets for chemoprevention have been elucidated by previous studies and are outlined in Figure 1.

Oral therapies for skin cancer chemoprevention in photodamaged skin

Retinoids

Retinoids, which are natural and synthetic derivatives of vitamin A, have anti-tumoral abilities as they regulate epithelial maturation, cellular differentiation, growth arrest, and apoptosis by activating nuclear retinoid receptors. The use of oral retinoids for chemoprevention of SCC has been extensively investigated in the transplant population, and current guidelines advocate for their use in patients at high risk for developing multiple, invasive, or metastatic SCC.[15,16]

There have been several clinical trials evaluating the use of oral retinoids as chemoprevention for NMSC. The largest double-blind, randomised controlled trial to date included 2297 patients and demonstrated that oral retinol 25,000IU daily reduced numbers of new SCCs (hazard ratio [HR] 0.74, p=0.04) but did not affect numbers of new BCCs (HR 1.06, p=0.36).[17] Furthermore, a nested cohort study conducted by Nijsten and Stern in 135 psoriasis patients demonstrated that oral retinoid use was associated with a reduction in new SCCs when compared to that patient's own tumour experience while not using retinoids with an incidence rate ratio of 0.79 (95% CI 0.65-0.95) but showed no significant association between retinoid use and BCC.[18] George and colleagues published a prospective open randomised crossover trial on 23 renal transplant recipients with a history of NMSC. Patients were crossed over at the end of one year, and 47.8% completed the two-year trial. The number of SCCs observed in patients treated with acitretin 25 mg daily or second daily was significantly lower than that in the drug-free period (p=0.002) and non-significantly reduced BCCs.[19] Bavinck and colleagues performed a double-blind, randomised

Figure 1: *Proposed candidates for chemoprevention*[14]

Excessive UVR exposure	Immunosuppressed	History of NMSC	Genetic syndromes	Exposures
• Severe photodamage	• Organ transplant recipients	• >5-10 NMSC per year	• Xeroderma pigmentosum	• PUVA
• Multiple AKs	• Chronic immunosuppressive therapies	• Increased turnover of NMSC	• Albinism	• Chronic radiation dermatitis
	• Haematological malignancies	• Multiple NMSC in high risk locations	• Recessive dystrophic epidermolysis bullosa	• Trauma
	• Human Immunodeficiency Virus	• Metastatic NMSC	• Nevoid BCC syndrome	• Extensive burns
		• Eruptive keratoacanthomas	• Epidermodysplasia verruciformis	
			• Bazex syndrome	
			• Rombo syndrome	

placebo-controlled trial on 44 renal transplant recipients with more than ten keratotic skin lesions assessing the efficacy of 6-months' treatment with acitretin 30 mg daily. Of the 48 assessable patients, the authors demonstrated that oral acitretin was significantly more effective than placebo at preventing NMSC (p=0.01) and reducing keratotic lesions without adversely impacting renal function.[20] Similarly, a study by McKenna and Murphy in the Royal Infirmary, Edinburgh, with 16 renal transplant patients who received oral acitretin 0.3 mg/kg daily for five years showed that new NMSCs were reduced during the treatment period compared to the pre-treatment period.[21]

These studies suggest that oral retinoids are likely to be effective in preventing SCCs and conceivably effective in preventing BCCs and reducing AKs. The use of oral retinoids is limited by their relatively poor tolerability and side effects which are dose dependent such as mucocutaneous dryness, hair loss, hypercholesterolaemia, hypertriglyceridemia, liver toxicity, skeletal demineralisation/hyperostosis, increased intracranial pressure and teratogenicity.[22] Therefore, oral retinoid use for the prevention of NMSC is generally limited to high-risk patients.

Nicotinamide

Nicotinamide is a water-soluble form of vitamin B3. The chemoprophylactic effect of nicotinamide is postulated to occur as it replenishes cellular energy[8], reduces inflammation[23], enhances DNA repair[24], and reduces UV-immunosuppression.[25]

In a phase 2 double-blinded randomised control trial published in 2012, 76 immunocompetent volunteers with ≥4 AKs were allocated to receive 500 mg of nicotinamide once (n=41) or twice daily (n=37) for four months, or placebo. The primary endpoint of the study was AK count. After two months, there was a 35% reduction in AK count in the group on nicotinamide 500 mg twice daily (p<0.0001) and a 15% reduction in AK count in those on nicotinamide 500 mg once daily (p=0.046) compared with placebo. At four months, there was a 35% reduction in AK count in those taking nicotinamide 500 mg twice daily (p=0.0006) and a 29% reduction in AK count in those taking 500 mg once daily (p=0.005) compared with placebo. The study also found that nicotinamide reduced AK count regardless of whether a patient had many AKs at baseline or only a few. While not a primary endpoint, the authors pooled the data from the two studies (nicotinamide 500 mg once daily and nicotinamide 500 mg twice daily) and noted that in the nicotinamide group, there was only four new NMSC (2 BCCs and 2 SCCs), compared with 20 new NMSC in the placebo group (12 BCCs and 8 SCCs), representing a relative rate of 0.24 (p=0.010).[26]

A phase 3 double-blind, randomised control trial conducted by Chen and colleagues was published in 2015, assessing 386 participants who had at least two NMSC in the preceding five years. Participants were allocated to receive nicotinamide 500 mg twice daily or placebo for 12 months assigned in a 1:1 ratio. The primary endpoint was the number of new NMSC. The study showed that at 12 months, the rate of new NMSC was lower by 23% in the nicotinamide group compared with placebo (95% CI 4-38, p=0.02). There was a 20% reduction in BCCs in the nicotinamide group compared with placebo (95% CI -6-49); however, the result was non-significant (p=0.12), and a 30% reduction in new SCCs (95% CI 0-51, p=0.05). The number of AKs was 13% lower in the nicotinamide group compared with placebo at 12 months (p=0.001). There was nil significant difference between the number or type of adverse events during the 12-month intervention period and no evidence of benefit after nicotinamide was discontinued.[27]

Therefore, nicotinamide seems to be well tolerated, and at the cost of $5-10 per month, appears to be a cost-effective method to protect against the development of NMSC and AKs in photodamaged skin.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Prostaglandin E2 (PGE2) has been implicated as a mediator of UVR induced skin damage[28] and enhances proliferation of keratinocytes by activation of growth-inducing pathways, including epidermal growth factor receptor (EGFR) and cyclic adenosine monophosphate production.[29] Further, UVR-induced PGE2 contributes to UVR-induced immunosuppression.[30] Inflammation and increased expression of cyclooxygenase (COX)-2 enzyme have been shown to be associated with NMSC.[31] COX-2 produces prostaglandins, including PGE2.

A 2020 meta-analysis that combined 26 original studies (223,619 cases and 1,398,507 controls) showed that NSAIDS and non-selective COX inhibitors were significantly associated with a reduced risk of skin cancer in the general population. Skin cancer was defined as NMSC, BCC, SCC or melanoma. The effect size (ES) for NSAIDs was 0.944 (95% CI 0.897-0.944, p=0.027) compared with ES=0.928 for non-selective COX inhibitors (95% CI 0.872-0.987, p=0.017). In contrast, there was no evidence that selective COX-2 inhibitors had such an effect (p=0.285). Eleven studies were combined to assess the effect of NSAIDs on BCC risk (ES=0.926, 95% CI 0.870-0.985, p=0.015) and the effect of non-selective COX inhibitors on the risk of BCC (ES=0.943, 95% CI 0.892-0.997, p=0.037). Similarly, there was no association between selective COX-2 inhibitors and BCC in the same population (p=0.683). Ten studies were combined to assess the effect of NSAIDs on SCC (ES=0.875, 95% CI 0.792-0.966,

p=0.008), and nonselective COX inhibitors (ES=0.903, 95% CI 0.831-0.983, p=0.018). Again, selective COX-2 inhibitors did not appear to prevent the development of SCC (p=0.292). However, this study was limited by significant heterogeneity and limitations of mechanistic classification due to available data provided from original articles.[32]

Therefore, there is evidence that oral NSAIDS, including non-selective COX inhibitors, may reduce the rates of skin cancer, including SCC and BCC. These drugs are likely photoprotective due to their ability to protect the immune system from UVR and limit UVR-induced keratinocyte growth. However, NSAIDs are known to be associated with significant side effects such as gastrointestinal toxicity, renal toxicity, and major cardiovascular events[33], which limit their potential widespread use as a chemopreventive agent for NMSC.

Difluoromethylornithine

Difluoromethylornithine (DFMO) is a medication used to treat hirsutism. DFMO inhibits ornithine decarboxylase, which is a rate-limiting enzyme in the synthesis of polyamines.[34] Ornithine decarboxylase is induced by UVB radiation and is upregulated in skin tumours as compared to normal skin.[35] Polyamines regulate cell survival, and increased levels of polyamines are associated with NMSC carcinogenesis.[35]

An animal study in mice demonstrated that oral DFMO prevented UVR-induced immunosuppression as well as skin cancers.[36] A double-blind, randomised controlled trial with 291 patients who received oral DFMO 500 mg/m^2/day for 4-5 years found a non-significant trend toward reduced new NMSC (260 versus 363 NMSC, p=0.069), though it did demonstrate a significant reduction in new BCCs (163 versus 243 BCCs, p=0.03). There was little difference in regard to the development of new SCCs.[37]

The use of oral DFMO as a chemopreventive agent is limited by clinically significant side effects, including ototoxicity.[38]

Vitamin D

Vitamin D is a fat-soluble vitamin that is essential for bone development. It has been shown to be anti-proliferative, activates apoptotic pathways, and inhibits angiogenesis.[39] There have been observational studies[40] and a randomised, controlled trial[41] that suggest vitamin D reduces overall cancer incidence in humans. A nested case-control study found that patients with the highest quintile of vitamin D had 47% lower odds of having a history of NMSC when compared to those with the lowest quintile of vitamin D (p=0.026).[42] Further randomised controlled trials are necessary to determine if vitamin D effectively reduces NMSC incidence in humans.

Selenium

Selenium is an essential dietary trace element. Selenium has been shown to prevent UVR-induced carcinogenesis in mice.[43] Case-control studies have shown that low plasma selenium was associated with NMSC[44] and melanomas.[45] A prospective cohort study found that baseline serum selenium was inversely associated with both BCCs and SCCs.[46] However, a multicentre, double-blind, randomised controlled trial with 1,312 participants found that oral selenium at the dose of 200 mcg daily did not significantly reduce BCCs or SCCs.[47]

Plant-derived products

Polypodium leucotomos (PL) is a tropical fern from the Phlebodium genus found in Central and South America. PL contains polyphenolic compounds, mainly benzoate and cinnamate, and 4-hydroxycinnamic acid (caffeic acid), which inhibits UV-induced peroxidation and production of NO, while its derivative, ferulic acid, is a UV photon acceptor. PL extracts have multiple beneficial properties by protecting tissue damage and limiting inflammation. PL supplementation has been shown to reduce UV-induced inflammation, facilitate the removal of photoproducts (CPDs), decrease UV-mediated oxidate DNA mutations, and has some protective effects against photoaging and PUVA induced phototoxicity. Therefore, PL extracts could have significant implications in skin cancer prevention. Furthermore, pharmacological surveillance of oral PL treatments conducted in Spain and South and Central America shows that PL is well absorbed and has no recognisable toxic effects. However, the necessary dosage of PL extracts are yet to be investigated, and large scale randomised controlled trials are lacking.[48]

An Australian study has suggested the protective role of plant-based dietary products by showing that humans with a history of skin cancer showed a decreased risk of SCC tumours for high intakes of leafy green vegetables (RR=0.45, 95% CI 0.22-0.91, p=0.02).[49] Another Australian study published in 2009 by Hughes and colleagues performed a community-based study of 1119 participants showed that AK acquisition decreased by 27% (RR=0.73, 95% CI 0.54-0.99) in those with the highest consumption of wine (average of half a glass per day).[50]

Garlic has been reported to have anti-tumoral properties, including the inhibition of skin cancer. Aged garlic extract has increased stability and is more consistent in composition compared to raw garlic juice whilst still retaining biological activity. When aged garlic was used to supplement the diets of mice, it was found to reduce UVR-induced systemic suppression of hypersensitivity from 48% to 19% and had a moderate protective effect against oedema.[51] Since garlic protected from cis-urocanic acid induced immunosuppression it has been suggested to work

by antagonising the effect of this UVR induced immunosuppressive mediator.

Tomatoes contain high concentrations of lycopene. Lycopene is a carotenoid that works as an effective quencher of singlet oxygen. When given orally to humans, lycopene provides some protection against UVR induced erythema.[52] A randomised control study on 20 healthy women who ingested 55 g tomato paste (16 g lycopene) showed reduced UVR induced erythema, UVR-induced matrix metalloproteinase-1 production, and mitochondrial DNA damage.[53]

Goji berries (Lycium barbarum) are used in traditional Chinese medicine and are rich in antioxidants. A study by Reeve and colleagues[54] found that Skh:hr-1 mice fed 5% goji berry juice in their water had reduced UVR-induced oedema and immunosuppression. Although the active ingredient that provided the photoprotective effect was not ascertained, the authors found that goji berry juice decreased UVA-induced lipid peroxidation.

Pomegranate fruit has also been shown to be photoprotective when fed to Skh:hr-1 mice. Pomegranate has antioxidant and anti-inflammatory properties, inhibiting UVB-induced oxidation of lipids and proteins, epidermal hyperplasia, and inflammation of the skin. Pomegranate is able to prevent UVR-induced activation of multiple signal transduction pathways, including COX-2 and inducible NO synthase.[55]

Monoterpenes include both perillyl alcohol and limonene. Perillyl alcohol is found in the oils of plants such as cherries, lavender, spearmint, and peppermint, while limonene is found in the peels of citrus fruits. Monoterpenes have been found to enhance the repair of photoproducts (CPDs) in cells.[56] A case-control study on 470 participants found that consumption of citrus peel reduced SCC risk (OR=0.66, p=0.03).[57]

Polyphenols are found in various plants, including most legumes, many grains, some fruits, vegetables, honey, red wine, chocolate, coffee and green tea. Polyphenols have an antioxidant, anti-inflammatory and immune protective properties. Many studies demonstrate the power of polyphenols as a photoprotective agent.[58,59]

The stimulant compound caffeine, which is structurally similar to adenosine and acts as an antagonist of adenosine receptors[60], has been shown to inhibit UVB radiation-induced carcinogenesis in mice.[61] Observational studies in humans have shown that those with the highest quintile of caffeine compared to those with the lowest quintile of caffeine intake had a reduced BCC risk (RR=0.82 for women and 0.87 for men, p<0.0001) although there was no association with SCC or melanoma.[62] This finding has been mirrored in other observational studies.[63] However, this finding was not replicated in two case-control studies.[64,65]

Animal-derived products

Carnosine (b-alanylhistidine) is a histidine-containing dipeptide. Carnosine is found in high concentrations (1-20 mM) of mammalian muscle and brain and, therefore, is supplied by dietary intake of meat or poultry. When used as a dietary supplement, carnosine has been shown to reduce UVR-induced systemic immunosuppression in mice from 65% to 17% suppression.[66] While studies have not elucidated how carnosine mediates its photoprotective effect, it has antioxidant properties. In contrast, diets high in meat and fats are associated with a higher risk of SCC.[67] Therefore, while carnosine could be photoprotective, other animal meat or fat components may promote UVR-induced skin cancers.

Similarly, dietary butter fed to Skh:hr-1 mice has been shown to protect against UVR induced suppression of contact hypersensitivity, seemingly due to the fatty acid composition of the butter.[68]

Diets rich in omega-3 fatty acids have been shown to be protective against UVB radiation-induced skin carcinogenesis in mice as mice fed high-fat fish oil in their diet had increased latency before developing UVB-induced skin cancer and a reduced incidence of the tumours, partially due to a reduced inflammatory response.[69] A community-based study in Queensland found that people with the highest consumption of oily fish (average one serving every five days) compared with those with minimal intake had a 28% reduction in AK acquisition (RR=0.72, 95% CI 0.55-0.95).[50] Rhodes and colleagues published a non-randomised study in 1995 which showed that humans who received supplementation of fish oil rich in omega-3 fatty acids reduced both UVA and UVB radiation induced inflammation, possibly by lowering PGE2 levels.[70] Pilkington and colleagues published a randomised controlled trial of oral omega-3 supplementation in 79 volunteers and showed a photo immunosuppressive effect, postulating that this may translate into a chemopreventive role.[71]

These studies provide evidence that while animal-derived products do not protect from UVR, fats found in oily fish and other animal-derived products such as carnosine are likely to be photoprotective.

Future direction

Several novel agents have been proposed for chemoprevention; however, further studies are required to support their use.

Capecitabine is a prodrug of fluorouracil (5-FU) that has shown efficacy in the treatment of SCC. As a monotherapy, administered orally at a dose of 1 g/m^2 divided into two daily doses on days 1-14 of a 21-day treatment cycle in 14 organ transplant recipients with recurrent NMSC, the difference in incidence rates of SCC, BCC, and AK before and after treatment were reduced by 0.25, 0.02, and 2.08 lesions per month with a p-value of 0.048, 0.844, and 0.151 respectively. Six of the 14 patients experienced grade 3-4 toxicities, including mucositis, hand-foot syndrome, fatigue, nausea, diarrhoea, hyperuricemia, and anaemia, requiring dose reduction or cessation of therapy.[72]

Afamelanotide is an analogue of alpha-melanocyte-stimulating hormone (α-MSH) with higher potency and longer action than the naturally occurring hormone. UVB induces the synthesis of melanin in melanocytes through the release of α-MSH from cutaneous melanocytes and keratinocytes. The effect is produced after UVB has already caused significant damage to keratinocytes. By administering synthetic α-MSH, there is an intended photoprotective effect as melanin levels are increased. Clinical trials are currently underway assessing the efficacy of afamelanotide in reducing the number of AKs and SCCs in organ transplant recipients.[73]

EGFR inhibitors are used in the treatment of non-small cell lung cancer, colorectal cancer, and SCC. Several antitumoral agents that block the EGFR (e.g. erlotinib, gefitinib) and anti-EGFR monoclonal antibodies (e.g. cetuximab, panitumumab) are currently being investigated as a treatment for advanced or recurrent NMSC.[74]

Conclusions

Overall, there have been multiple advances in the secondary prevention of NMSC with oral therapies, which are of increasing importance in light of the growing incidence and morbidity of NMSC. There is considerable evidence that oral therapies and food substances can provide additional photoprotection. Experimental studies have elucidated how sunlight damages skin and has led to the discovery of well-tolerated photoprotective agents. While primary prevention remains paramount, for some higher-risk candidates, secondary prevention with chemopreventive agents is required. There is good evidence for the use of nicotinamide which is well tolerated and cost-effective. Other agents such as retinoids have strong evidence behind their use but are limited to select populations due to their side effect profile.

Similarly, while DFMO has shown an effect in reducing new BCCs, it is limited by its side effect profile. Further studies regarding the efficacy and required therapeutic regimen for NSAIDs, vitamin D, selenium, and plant and animal-derived products are required. Multiple new agents are currently being investigated as chemopreventive agents for NMSC, including capecitabine, afamelanotide, and EGFR inhibitors.

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Photodynamic Therapy for Superficial Sun Damage

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OUTLINE: In sun-damaged skin photodynamic therapy (PDT) can have both therapeutic medical and cosmetic actions. PDT is effective for the treatment of actinic keratosis, superficial (+/- thin nodular) basal cell carcinoma and Bowen's disease where it is a good option particularly in patients presenting with actinic field cancerisation skin changes. PDT has also been used off-label for a range of skin diseases along with cosmetic dermatology particularly for photorejuvenation.

Sun damage, from UV radiation exposure, is responsible for a range of skin changes characterised as photoaging along with the formation of precancerous and cancerous skin lesions. Aesthetic PDT indications include dyspigmentation, solar lentigines, fine lines and wrinkles, mottled hyperpigmentation, telangiectasia, erythema, skin roughness and skin texture changes including sallowness and actinic elastosis.

Laser-assisted PDT involves the skin's laser pretreatment to enhance drug delivery of the photophore. This can be utilised to enhance both actinic keratosis response, and photorejuvenation aesthetic outcomes.

Key steps in PDT involve skin preparation (fractional ablative laser in laser-assisted PDT), application of photophore (5-aminolevulinic acid or methyl aminolevulinate), occlusion, an incubation period then illumination. Illumination can utilise light-emitting diodes, laser, intense pulsed light, sunlight, or a combination of light sources.

The beneficial effects from PDT include upregulation of collagen production and decrease of elastotic material in the dermis. Although traditional PDT is not as effective as more invasive techniques for the treatment of deep wrinkles and severe skin laxity, repeated treatments and in particular laser-assisted PDT can be utilised to enhance aesthetic benefits.

KEYWORDS: photodynamic therapy, photoaging, photorejuvenation, laser-assisted drug delivery, intense pulsed light

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Introduction

Aging is a multifactorial process influenced by environmental, hormonal and genetic factors. This results in functional and aesthetic changes in the skin. The term photoaging highlights the importance sunlight and particularly ultraviolet radiation play in skin aging[1] with its visible changes most evident in chronically sun exposed areas including the face, neck, décolletage, dorsum of hands and forearms.

Sun damage is characterised by fine lines and wrinkles, roughness, dryness, laxity, sallowness, dyspigmentation, erythema and telangiectasias and can be associated with premalignant and malignant skin lesions. These highly visible areas are frequently the therapeutic target for aesthetic improvements.

Photodynamic therapy for skin rejuvenation

Photodynamic therapy (PDT) is an established treatment for actinic keratosis (AK), superficial basal cell carcinoma and Bowen's disease and utilised for both focal and field cancerisation treatments. The significant improvement in the signs of skin aging observed has resulted in clinical studies into PDT's aesthetic benefits utilising both 5-aminolevulinic acid (ALA)-PDT[2,3] and methyl aminolevulinate (MAL)-PDT.[4] PDT has become an option to consider for skin photorejuvenation of sun-damaged skin because of its medical and aesthetic effects.

Aesthetic PDT indications include dyspigmentation, solar lentigines, fine lines and wrinkles, mottled hyperpigmentation, telangiectasia, erythema, skin

roughness and skin texture changes including sallowness and actinic elastosis.[5,8]

The published studies utilise a range of regimens that can differ from licensed protocols for the treatment of AK and non-melanoma skin cancer. PDT is not licensed for cosmetic indications and there are no standardised guidelines for PDT in skin rejuvenation. Illumination devices have on their own been shown to improve the clinical signs of photoaging and include vascular laser (pulsed dye laser [PDL]) and intense pulsed light (IPL) which can have a synergistic effect on clinical outcome[9] as demonstrated by split face studies utilising IPL and PDL.[5,8] In laser-assisted PDT, the utilisation of fractional carbon dioxoide (CO_2) laser and/or Erbium:YAG (Er:YAG) laser prior to performing PDT increases photophore delivery to enhance therapeutic PDT AK benefits and have their own direct and potentially synergistic cosmetic skin benefits.

Mechanism of action

PDT involves a photochemical reaction mediated through the interaction of photosensitising agents, light and oxygen. After application of the ALA or MAL prodrug, there are significant differences in subsequent porphyrin accumulation seen between various tissues and cell types. Epidermal, sebaceous and in particular dysplastic and neoplastic cells accumulate both ALA and MAL. This accumulation also occurs in blood vessel walls and in association with melanin. These are all important photorejuvenation and actinically damaged skin targets.

Most cells can transform ALA or MAL into porphyrins. When an overwhelming quantity of the upstream porphyrin substrates (ALA) is supplied as in PDT, the lipid-soluble protoporphyrin IX (PpIX) is predominately accumulated in the target cells. This occurs because PpIX is the substrate for mitochondrial ferrochelatase, a rate-limiting enzyme in the porphyrin pathway. PpIX is largely responsible for the oxygen dependent phototoxicity reaction utilised therapeutically in PDT.[10]

After incubation, light is utilised to activate the photosensitiser (PpIX) in the presence of oxygen. The Soret band (approximately 405-420 nm blue light) represents the light excitation peak of PpIX, followed by four much smaller peaks (known as Q bands). Q bands include green, yellow, orange and red (~635 nm) peaks. Blue light is about 50 times more effective for activating PpIX than red light but has less depth of penetration (1-2 mm for blue vs ~4 mm for red).[11] This makes blue light highly effective for epidermal and upper papillary dermal targets, and red light potentially better for deep dermal penetration and targeting.[11]

PDT has an oxygen-dependent direct phototoxic effect on target cells and as for skin cancer indications, when used aesthetically, a reduction in epidermal atypical cells is observed. PDT has been shown to modify cytokine expression, induce immune-specific responses and cause vascular damage. There is a significant increase in skin thickness after MAL-PDT with an increase in collagen and procollagen type I and III, along with a reduction in elastotic material and dermal inflammation.[10] An increase in transforming growth factor-beta and a decline in matrix metalloproteinases (MMP-1,-3 and MMP-12) has been observed, consistent with increased collagen synthesis and reduced collagen and elastin degradation.[9] Markers of collagen synthesis peak around 30 days after PDT and decline to day 60.[9] Cosmetic benefits after utilising 0.5% liposome-encapsulated ALA suggest a clinical inflammatory or phototoxic response is not required for all cosmetic benefits.[13]

Pharmacology of ALA and MAL

Both ALA and MAL are prodrugs and require cell uptake and transformation into their active form - PpIX - within mitochondria. PpIX is the photosensitiser which in the presence of oxygen is activated by light leading to its phototoxic effects targeted on cells and tissues that have absorbed, activated and accumulated the prodrug.

ALA is hydrophilic while MAL is lipophilic. The stratum corneum, the outermost layer of the skin, presents the main barrier to topical absorption particularly for hydrophilic compounds. Skin preparation prior to their application is required to enhance penetration including topical keratolytic agents, curettage, abrasion, acetone and more recently fractional CO_2 or Erbium laser in laser-assisted PDT.

20% ALA has been most utilised in aesthetic published studies and in the same concentration used to treat AK in the US (Levulan Kerastick Dusa Pharmaceuticals, Wilmington, MA).

Laser-assisted drug delivery

Laser-assisted drug delivery (LADD) is a promising drug delivery technique to enhance the efficacy of local skin treatments. This involves (1) laser pretreatment followed by (2) topical drug application aiming to (3) increase and target the amount of drug that reaches the appropriate skin component to improve treatment efficacy. The best evidence for LADD is currently for PDT and AK (ALA/MAL, Figure 1 and 2).[14] The stratum corneum is a tough barrier and its lipophilic nature makes it a formidable barrier particularly for hydrophilic (ALA) or large substances. Ablative fractional lasers (AFL) are an effective method used to overcome the epidermal

barrier. Absorption benefits plateau between 5-10% density, with densities above 5% exerting only a minimal additional effect.[15] Greater density beyond 5% however can have aesthetic benefits but is associated with greater severity skin reactions and downtime. For hydrophilic molecules like ALA, greater laser channel depth further enhances accelerated and increased depth of drug deposition in skin layers (100 µm-750 µm-1500µm: corresponding to the dermoepidermal junction-superficial dermis-mid dermis) with the coagulation zone seen with the CO_2 laser providing a sponge to soak and draw in hydrophilic molecules and also provide a drug reservoir from which diffusion occurs. For lipophilic drugs such as MAL, deeper laser skin channels beyond 300 µm are not associated with any further enhanced absorption. ALA/MAL should be applied within 30 minutes before significant pore reduction starts to occur.

The disadvantages of laser-assisted PDT include greater severity skin reactions, discomfort, exudate, and more frequent pustular skin reactions, but also a greater degree of tissue remodeling and cosmetic outcomes including texture, dyspigmentation along with enhanced field cancerisation improvement (Figure 3 and 4). When utilised away from the pilosebaceous gland rich face, such as the neck, decolletage and hands, AFL density greater than 5% and the use of deeper channels should be utilised with care and caution.

Non-ablative fractional laser (including erbium glass and thulium) along with skin needling have also been utilised however further study and quantification is required regarding LADD and PDT with these devices.

Clinical assessment and patient selection

As with all cosmetic treatments appropriate patient selection is key including managing patient expectations and the strict need for sun avoidance in the 48 hours following treatment.

PDT is best utilised in fairer skin types. A reduced PDT effect is seen in highly pigmented versus lighter skin clinically and in animal models. There is also a theoretically greater risk of post inflammatory hyperpigmentation in darker skin types. This reduces the benefits and increases the risks of aesthetic PDT when performed in darker skin types. Consideration also needs to be given to the light source utilised based on patient skin type and skin changes being targeted. Contraindications to PDT include porphyria, systemic lupus erythematosus and other photosensitivity dermatoses along with allergy to MAL or excipients.

Patient skin preparation

- Sun-protection before and after treatment assists treatment efficacy and reduces post-inflammatory pigmentation risk.
- To facilitate more even and effective skin absorption of ALA and MAL, skin care during the 2 or more weeks prior to treatment, where appropriate, should include either a topical α–hydroxy acid, salicylic acid, retinoid and/or urea cream. The authors commonly use a 4% lactic acid day and 10% lactic acid night cream for the face, neck or chest and a combination lactic acid (10%) and urea (10%) cream twice a day for the dorsum of hands and forearms, ceased the day before PDT treatment.
- A series of superficial chemical peels has also been utilised.
- Topical 5% 5-fluorouracil cream daily for 6 days has been shown to increase PpIX levels in AK and improves AK clearance response.[16]

Immediately before application of sensitizer

Topical anaesthetic cream should be considered prior to ablative fractional laser treatment for laser-assisted PDT.

Skin degreasing by wiping with gauze moistened with acetone (or alcohol) can be performed particularly if using hydrophilic ALA rather than hydrophobic MAL to enhance its penetration. This is followed by:

- Mechanical peeling such as sandpaper (or microdermabrasion) and/or
- Light curettage
- For laser assisted PDT this is followed by ablative fractional laser (AFL) (Er:YAG or CO_2)

The authors usually combine curettage and AFL based on AK study data. Consider anti-viral herpes prophylaxis where indicated.

Laser-assisted PDT (AFL)

- Density 5%.
- Depth 100 µm-300 µm (deeper channels of added benefit for ALA but not MAL).

- Higher densities and deeper channels can be utilised for greater cosmetic benefits but are associated with greater severity skin reactions.
- CO_2 lasers produce a greater coagulation zone and may have drug delivery benefits over Er:YAG for hydrophilic molecules such as ALA.

Application of prodrug

Formulations include 16.8% MAL cream, and 20% ALA spray or ointment. This is followed by occlusion and incubation.

Incubation period

MAL-Non-daylight

- 3 hours (AK and NMSC)
- 2 hours (laser-assisted PDT)[15]
- Occlusion

MAL-Daylight

- 30 min (including laser-assisted PDT)

ALA

- 120 min
- 90 min (laser-assisted PDT)[15]
- 30-60 min purely aesthetic PDT (including laser assisted PDT)

This should be performed in a warm room with protection of treated areas from visible light. Occlusion should be routinely utilised during incubation to enhance photophore absorption (e.g., plastic cling film wrap).

Illumination (aesthetic PDT)

Multiple light sources have been used successfully including traditional PDT LED illumination and natural sunlight. For aesthetic PDT IPL is most commonly used in reported studies. PDL has also been reported. Some advocate use of multiple light sources during the same treatment such as IPL and/or PDL followed by LED.

Pulse durations in the millisecond range (IPL and PDL) compared to minutes with LED light have been associated with less pain.[17]

PDT with intense pulsed light

IPL is used in PDT photorejuvenation and has in split face studies been shown to be superior to IPL alone.[5,8] IPL PDT photorejuvenation benefits include improvement in crow's feet, tactile roughness, mottled hyperpigmentation, facial erythema, and telangiectasia. IPL systems emit light in the wavelength range of 400-1200 nm. Depending on the IPL system and handpiece this can variably span PpIX Soret band peak and its four smaller Q bands. The variety of IPL handpieces (with differing wavelength ranges) along with ability to vary pulse duration (single and double pulses), pulse interval, energy density, and number of passes, all enhance the ability to target different aesthetic skin changes but make comparing studies and devices used difficult.

Multiple IPL passes have been utilised and have been associated with better AK response.[18] PpIX skin fluorescence monitoring can be used to assist enhance PDT treatment.[19]

For photorejuvenation indications, the authors usually perform an initial IPL treatment pass with settings based on patient skin type, tanning and skin problem being targeted (e.g. telangiectasia, rosacea, photorejuvenation) using the appropriate IPL handpiece that incorporates 2-3 Q bands of PpIX. In patients with AK, multiple passes are performed including utilising a handpiece that includes the Soret band peak and all four Q bands. The number of passes performed is guided by monitoring PpIX skin fluorescence response (FluoDerm™ Denmark emitting wavelength: 400-420 nm; measuring excitation wavelength: 610-720 nm).[19] See Figures 1-4 for treatment examples.

Multiple treatment sessions of PDT with IPL may be performed. Based on PDT studies, treatment intervals of 2 or more months[9] can be considered for increased benefits and/or maintenance treatments. The treatment parameters for PDT with IPL should be ideally based on published studies and PDT settings validated for the device.

PDT with red (and blue) light LED

PDT with red LED light has been associated with improvement in mottled pigmentation, fine lines, roughness and sallowness (but not coarse wrinkles, telangiectases, and facial erythema).[9] Similar results have been reported with blue light in regard to skin photoaging.[9] Differences in red and blue light in regard to depth of skin penetration and photophore activation and whether these affect cosmetic outcomes have not been specifically addressed by a controlled study.

PDT with pulsed dye laser

Activation with 595 nm PDL, which corresponds to the third (orange) Q band of PpIX, has shown greater global photodamage improvement than blue light including

telangiectasia and erythema.[20] This is similar to the synergy observed with PDT-enhanced IPL.

Pain management

Premedication and topical anaesthetic prior to AFL for laser-assisted PDT should be considered.

The application of ALA (and less so MAL) after AFL leads to brief but intense stinging; the authors offer nitrous oxide analgesia to address this when treating larger areas. Pain with conventional LED (greater with red versus blue light) illumination generally develops quickly after the start of irradiation, cumulates during irradiation, and decreases over several hours following irradiation. Pain is generally less severe for aesthetic millisecond IPL activation compared with LED illumination.[15] Cryo cooled air during and after irradiation can be utilised and nerve blocks considered. Post treatment cooling with saline compresses, cold cream and/or ice packs can also be considered.

Summary

PDT is a promising treatment for sun-damaged skin combining both medical and aesthetic benefits. Licensed PDT protocols for AK field treatment are associated with cosmetic skin benefits. PDT should also be considered for the treatment of skin aging and photoaging. Pre-treatment with fractional ablative laser (best validated for CO_2) represents an advanced option that improves photosensitiser absorption and therapeutic outcomes, including AK clearance and photorejuvenation. For solar lentigo, dyschromia, telangiectasia, erythema, and fine lines, IPL illumination has been best studied. Further studies are required - including those that compare light sources, PDT therapy protocols for photorejuvenation - to better quantify laser-assisted PDT for aesthetic photoaging treatment outcomes.

Figure 1
Baseline actinically damaged scalp and forehead of a 77-year-old. Field cancerisation including actinic keratoses, in situ squamous cell carcinoma. Laser-assisted PDT performed as part of his skin cancer management.

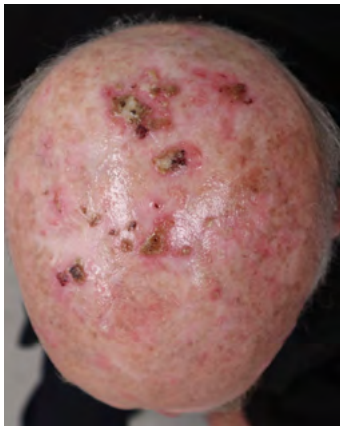


Figure 2
Week 5 post laser-assisted PDT treatment. 5% CO_2 fractionated laser with 300 µm depth channels to field, targeting of clinical lesions with 700 µm depth channels, 16.8% MAL, 120 min incubation, illumination IPL, 4-5 passes 400-720 nm range, single pulse 30 ms 3.4 J/cm² indicated for PDT. Fluorometer® Denmark pre and post skin fluorescence measurements utilised to guide and assess photophore activation. Good field benefits have been maintained 2 years post single treatment.

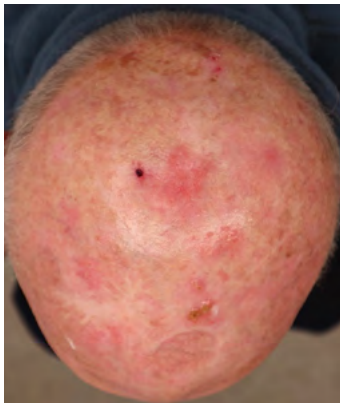


Figure 3
Baseline face and neck of a 62-year-old female with skin changes of photoaging.

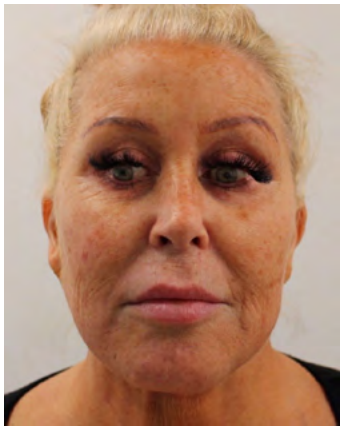
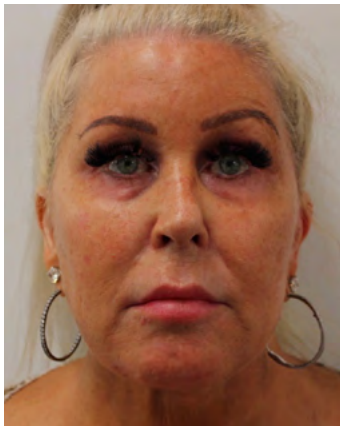


Figure 4
Post single laser-assisted PDT treatment. 5% CO_2 fractionated laser with 300 µm depth channels, 20% ALA, 90 min incubation, IPL, first pass 555-950 nm range, double pulses of 2.5 ms, 10 ms pause, 9.6 J/cm² indicated for rosacea, telangiectasia and photorejuvenation then 2nd and 3rd passes 400-720 nm range, single pulse 30 ms 3.4 J/cm² indicated for PDT.



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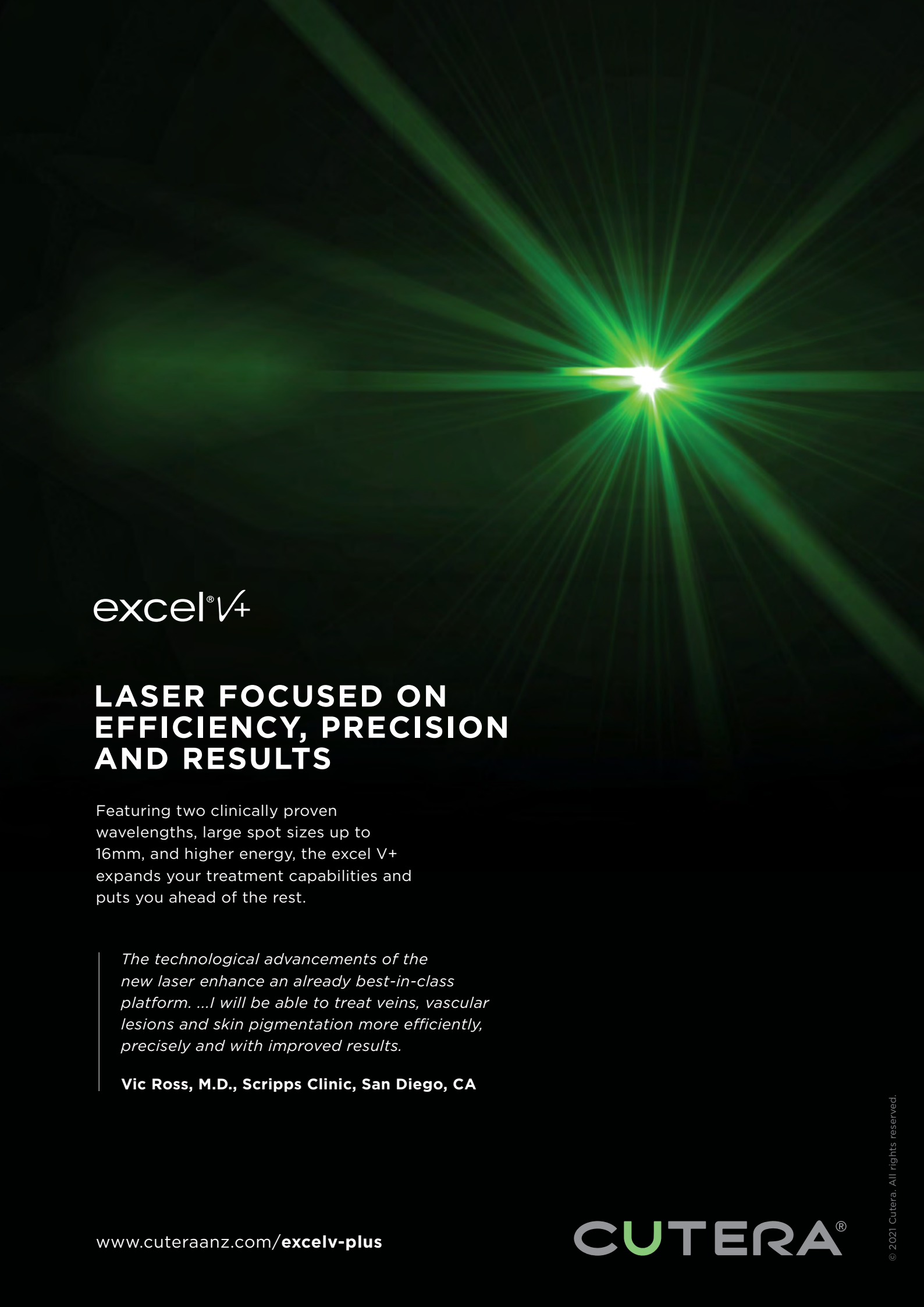

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Disclosures: *none*

OUTLINE: The skin absorbs ultraviolet (UV) radiation as the body's first line of defence against the sun and its harmful effects on cellular DNA. Over time, absorption of UV light results in permanent and visible changes on the skin, including dyschromia, increased vascularity, laxity, and rhytides. This article outlines the principles of using modern energy-based devices such as intense pulsed light (IPL), laser devices, and radiofrequency needling to treat common signs of photodamaged skin.

KEYWORDS: photodamaged skin, intense pulsed light, laser, fractional lasers, radiofrequency needling

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Introduction

Photodamage of the skin is caused by extrinsic exposure to ultraviolet A (UVA) (320–400 nm) and UVB (290–320 nm) light spectrums. Over time, UV radiation causes damage to the skin via free radical DNA damage, altered inflammatory pathways and abnormal elastotic protein formation.[1,2,3] As a result, collagen and elastin fibres become disorganised and reduce in number, whilst melanocyte and melanosome activity can be locally increased. These changes eventually result in the characteristic signs of photoaging including dyschromia, increased vascularity, skin laxity, fine lines and deeper rhytids. Whilst traditional therapies such as topical retinols, hydroquinone, chemical peeling, microdermabrasion and cosmetic injectables can effectively treat some aspects of photodamage, energy-based devices are now commonplace as either stand-alone treatments or in conjunction with other therapies. Their excellent safety profile and shorter recovery times have also made them popular with patients who report increased overall satisfaction with energy-based treatments.[4,5]

The benefits of light therapy to treat skin disorders can be dated back to ancient Egypt; however, it was not until 1903 when Niels Finsen received a Nobel Prize for his work using concentrated light radiation to treat cutaneous tuberculosis that the therapeutic benefits of light or light energy was beginning to be realised.[6,7]

While Finsen's discovery opened a whole new field of radiation medicine, it was not until the 1960s that the first working 694 nm Ruby laser came into use. During an investigation on the safety of low-level laser irradiation and the potential risk of skin dysplasia (which was later discredited), it was discovered to accelerate wound healing.[8,9] With the potential for enhanced skin repair and remodelling, subsequent murine and human studies identified several fundamental mechanisms responsible for enhanced skin repair. Mechanisms included enhanced cell respiration and mitochondrial ATP synthesis, reduced oxidative stress, and altered gene expression favouring cellular repair.[10]

By using light energy, either non-coherent (e.g. IPL) or monochromatic coherent (e.g. laser) light at specific wavelengths, clinicians can target skin cell types and tissue chromophores based on their absorption characteristics and principles of selective photo thermolysis.[11] Melanin, for example, has a relatively linear absorption spectrum ranging from 335 nm and decreasing exponentially to near-infrared wavelengths at 1100 nm. Thus, Q-switched and picosecond 532 nm, 670 nm and 1064 nm lasers can be effective in targeting melanin at several points along this line. Haemoglobin, however, has several peaks along the coefficient absorption curve, 418 nm, 542 nm, 577 nm and 1064 nm, which can be specifically targeted to cause optimal vascular ablation (Table 1).[11,12] Modern energy-based

devices can optimally cause cell lysis and protein denaturation with minimal surrounding tissue damage whilst associated biomodulatory responses enhance cell repair.

Hence, with an improved understanding of the deleterious effects of UV radiation on skin and the biophysics of energy-based devices, signs of photodamage can be effectively treated with sophisticated technologies such as IPL, non-ablative and ablative lasers.

Dyschromia

Q-switched nanosecond lasers, picosecond lasers and intense pulsed light

Chronic sun exposure is the primary determinant of the development of solar lentigines, a common presentation resulting in uneven skin colour and possibly texture. More common in Fitzpatrick skin type I-II,[5] solar lentigines should be carefully differentiated from other similar appearing lesions such as ephelides, lentigo simplex, familial lentiginoses, melanocytic naevi and melanoma.

Initially, treatment for solar lentigines had been limited to topical and physical therapies such as retinol, hydroquinone, chemical peeling, electrodesiccation or cryotherapy. However, energy-based devices now provide superior accuracy in treating excess pigmentation with minimal surrounding tissue damage. Lasers used to treat photopigmentation can be generally divided into three broad categories: (1) IPL and Q-switched nanosecond and picosecond lasers; (2) ablative lasers, and (3) fractional non-ablative lasers (e.g. Thulium 1927 nm laser).

Melanosome apoptosis occurs via selective photo thermolysis,[10] whereby a wavelength is selected to achieve maximum absorption of light and, therefore, heat energy by the target chromophore, in this case, melanin. Melanin's relatively broad light absorption spectrum (250–1200 nm) crosses both the vascular (haemoglobin) and water spectrums, offering unique advantages and disadvantages in its treatment. However, it is generally accepted that wavelengths of 532 nm (potassium titanyl phosphate; KTP), 690 nm (Ruby), 755 nm (Alexandrite) and 1064 nm neodymium yttrium aluminium garnet (Nd:YAG) lasers are most useful for the treatment of epidermal and dermal pigmentation.

Due to melanin's small particle size (sub-micrometre), ultra-short pulses of light are now considered optimal when targeting pigment. Q-switching, invented in 1962, allows a higher number of excited photos to build up using Pockel cells with in the laser. These contain crystals, which can propagate light and then, very quickly using an electric switch, be turned opaque to allow that light to escape momentarily.[13] Q-Switched (QS) nanosecond lasers, including the QS Ruby, QS Alexandrite and QS Nd:YAG, have produced excellent results in treating epidermal and dermal pigmentation.[14,15,16]

Newer picosecond lasers in 532 nm, 755 nm and 1064 nm wavelengths can deliver pulse durations of 300–900 picoseconds. Their mechanism of action is via photoacoustic damage rather than photothermolysis.[17] Due to their increased selectivity, treatments are safer, particularly for individuals with darker skin types (III-VI) who have previously been excluded from energy-based light therapies due to the risk of post-inflammatory hyperpigmentation and poor-quality response to treatments.

For most epidermal pigmented lesions such as solar lentigines, Q-switched nanosecond and picosecond lasers between the range of 500–755 nm are utilised.[5] However, IPL is versatile with the ability to target pigmentation and increased vascularity at the same time. Furthermore, due to larger spot sizes, areas of the body, notably legs, decolletage, dorsal hands and arms, can be treated more efficiently.

IPL differs from laser systems by emitting broadband (500–1200 nm), non-coherent light, then using filters to select the light wavelengths which are emitted to the skin. However, a significant limitation is a requirement for high contrast levels between the target areas of concern and the background skin. This requirement, therefore, limits treatments for dyschromia with IPL mainly to Fitzpatrick skin-types I-II.

Occasionally ablative resurfacing lasers may be used for discrete lentigines, especially those which are palpable. The CO_2 and Erbium:YAG lasers may both be employed in this setting. The risk of hyper and hypopigmentation increases with ablative devices in this setting and must be used with care.

Increased vascularity

Pulse dye laser, KTP laser and intense pulsed light

Lighter skin types will often present with considerable vascular changes as a result of photodamage. Therefore, careful assessment is required to ensure alternate diagnoses are not missed, including rosacea, seborrhoeic or photo contact dermatitis, systemic lupus erythematosus, and dermatomyositis, all of which may require further medical evaluation and systemic treatments. Typical vascular changes associated with photodamage include erythema, telangiectasia and poikiloderma.

Pulsed dye laser (PDL) with a wavelength of 585 nm or 595 nm, is considered the gold standard treatment for increased vascularity associated with photodamage. The mechanism of action involves selecting for the haemoglobin chromophore with enough fluence to cause coagulation of the blood vessel and formation of fibrosis permanently ablating the vessel. In telangiectasia, haemoglobin is the target chromophore found at various oxygenation states. Oxygenated haemoglobin (oxyhemoglobin) has several absorption peaks along the absorption coefficient curve, including 418 nm, 524 nm, 577 nm and 1064 nm.[5,12] Given that the first and second peaks overlap with important melanin absorption spectrums, the optimal target wavelengths have been established between 580 nm and 590 nm.

Once the appropriate wavelength has been selected a pulse duration based on the calibre of the vessel and subsequent thermal relaxation time will result in maximum thermal damage to the vessel with minimal surrounding tissue damage. When treating small but visible telangiectasia of less than 0.5 mm on the face, pulse duration may range between 0.45 to 3 ms.

The endpoint for telangiectasia is either the disappearance of vessels or purpura. Patients must be counselled on possible vessel rupture causing purpura lasting up to 7 days. However, this risk can be minimised with tissue cooling pre- and post-treatment and careful device settings.

Potassium titanyl phosphate (KTP) 532 nm lasers, Alexandrite 755 nm, Nd:YAG 1064 nm and IPL with vascular filters are also valuable devices for treating facial erythema and telangiectasia. KTP and newer lithium triborate (LBO) containing 532 nm lasers target oxyhaemoglobin closest to the 524 nm absorption peak, making them highly effective in targeting facial vascularities.[18] Greater absorption overlap with melanin, however, can result in more diffuse inflammation compared with other vascular lasers. Larger facial vessels usually require Nd:YAG 1064 nm laser, targeting deeper vessels of diameters greater than 0.5 mm. Longer pulse durations are selected to match tissue relaxation times of vessels ranging between 15–50 ms. Additional care is required to avoid coagulation of deeper arteries, such as the alar artery around the nose. The reduced risk of post inflammatory hyperpigmentation in patients with skin of colour is of added advantage.

IPL (500–1200 nm), similar to its use in treating dyschromia, has the advantage of larger spot sizes suitable for treating larger body areas and can be particularly useful in treating poikiloderma of Civatte of the neck.

Rhytides and laxity

Fully ablative laser resurfacing

Ablative laser resurfacing, primarily with the CO_2 or Erbium:YAG lasers, is often considered the gold standard for treating moderate to severe photodamaged skin and features such as rhytides, wrinkles and dyschromia.[19,20]

Ablative lasers vaporise tissue, exfoliate, cause tissue contraction and result in collagen synthesis. They produce significant improvements (Figure 1) with tone, texture, and pigmentation. They often require less treatment sessions but are also associated with prolonged recovery time and increased risk of complications and side effects.

Complications from ablative laser resurfacing include infection, prolonged erythema, hyperpigmentation, delayed hypopigmentation and scarring.

Patients need to be counselled regarding the length of healing after ablative resurfacing and potential complications, and if not suited, be directed towards fractional ablative or non-ablative resurfacing.

Fractional ablative resurfacing

Fractional ablative resurfacing involves delivering the CO_2 or Erbium:YAG laser energy in microscopic columns, or 'micro-thermal zones', to ablate segments of the skin while sparing intervening tissue. As the bulk of the skin surface is left unaffected, recovery time is significantly reduced.[5] It also allows for treating areas other than the face, darker skin types and compromised tissue (e.g. keloid and burn scars).

Improvements with fractional ablative resurfacing may be more modest than traditional ablative resurfacing. A study of fractional resurfacing versus fully ablative resurfacing with the Erbium:YAG laser for facial rejuvenation showed that mean epidermal thickness improved with just one ablative session, compared with four fractional sessions.[21]

Thus, treatment protocols generally require 2-6 treatments for significant improvements with photodamage, dyschromia and deep rhytides.

Fractional non-ablative resurfacing

Non-ablative fractional resurfacing (NAFR) relatively spares the epidermis while sending micro-thermal zones into the dermis. Depending on the wavelength, fluence and density, NAFR lasers may improve photodamage induced pigment, texture and fine lines by promoting collagen remodelling following controlled dermal injury (Figure 2).[22]

Commonly utilised wavelengths include the 1540 nm and 1550 nm Erbium:Glass and the 1927 nm Thulium.[23] More novel wavelengths include 1440 nm, which has shown efficacy for photodamage.[24]

The advantages of NAFR, and the reasons for its popularity, include the low downtime (typically 1-7 days), option to treat all skin types with less risk of dyschromia, and high safety profile with less risk of side effects and complications (Figure 2).

Results are more modest than fully ablative and fractional ablative lasers, and generally, a series of treatments spaced at least a month apart is recommended.[25]

Novel hybrid lasers

Lasers emerging in prominence in the market include hybrid devices, such as those incorporating ablative Erbium:YAG laser to vaporise 100 microns into the epidermis and non-ablative (1470 nm) settings to coagulate 100 to 700 microns to the epidermis and dermis.[23]

These allow for treatment of both epidermal photodamage and dermal remodelling, with less downtime than purely ablative lasers.

Radiofrequency microneedling

Microneedle fractional radiofrequency (MFR) has also become an option for skin rejuvenation in photoaging, particularly for wrinkles, fine lines and texture, as it too has less downtime and complications than ablative procedures.

MFR utilises radiofrequency energy through insulated or non-insulated microneedles, precisely delivering energy at the required depths and stimulating and inducing collagen modelling and regeneration.

MFR is particularly useful for darker skin types as it is less likely to provoke post-inflammatory hyperpigmentation than fractional lasers. A split-face study of Chinese women showed significant improvement in deeper rhytides, fine lines, pore size and skin texture, both related to photoaging and intrinsic aging.[26]

Summary

As a result of chronic UV radiation, signs of skin ageing become more visible with time, including dyschromia, increased vascularity, laxity and rhytides. Tissue chromophores such as melanin, haemoglobin and water can be selectively targeted by choosing the appropriate energy-based device and corresponding wavelength. In addition to selective photothermolysis, low-level irradiation also promotes cellular repair pathways and dermal collagen remodelling. Parameter settings must be selected with care and a good understanding of the effect on the target tissue for optimum safety and efficacy. In combination or alone, energy-based devices including IPL, laser and radiofrequency needling have become powerful and effective tools for treating photodamaged skin.

Table 1. *Skin tissue chromophores and corresponding energy-based devices*

Tissue chromophore	Energy-based device
Melanin 335 nm – 1100 nm	IPL 500 – 1200 nm Q-switched and Picosecond lasers 532 nm, 670 nm, 755 nm and 1064 nm
Haemoglobin 418 nm, 542 nm, 577 nm and 1064 nm	PDL 585 nm and 595 nm KTP 532 nm laser Alexandrite 755 nm Nd:YAG 1064 nm laser IPL 500 – 1200 nm laser
Water 1064 nm – 10,600 nm	Erb:YAG 2940 nm laser CO_2 10,600 nm laser Erbium:Glass 1540 nm and 1550 nm laser Thulium 1927 nm laser

Erb:YAG, Erbium-doped yttrium-aluminium-garnet; IPL, Intense Pulsed Light; KTP, potassium titanyl phosphate; Nd:YAG, neodymium:yttrium-aluminium-garnet; PDL, Pulsed Dye Laser; Q-switched, quality switched

Figure 1. *55-year-old female patient treated with combination IPL and Erbium:Glass 1550 nm for dyschromia, vascularity and texture*

Photograph courtesy of Dr S Manoharan

Figure 2. *65-year-old female patient treated with one session of fully ablative CO_2 resurfacing for lentigines, rhytids, tone and texture*

Photograph courtesy of Dr S Manoharan

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Commentary: Are Deeper Laser Treatments Advantageous in Treating Solar Dysplasia?

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OUTLINE: When it comes to solar dysplasia and epidermal ablation, is more necessarily better?

KEYWORDS: solar dysplasia, solar keratosis, fractional laser, 1927 nm thulium

Lim D. Commentary: Are Deeper Laser Treatments Advantageous in Treating Solar Dysplasia? Opin Prog Cosmet Dermatol 2021;1(3):48-49.

Here's a thought. An energy device that provides deep ablation should give the highest clearance for solar dysplasia. Logically, absolute ablation of the entire epidermis should give the best clearance and remission, as histologically solar keratoses are confined to the epidermis. The question is do we really need to abate the entire epidermis to give good results?

Initial reports of fully ablative laser resurfacing gave us exciting news. Clearances between 92-100% were obtained with CO_2 and erbium resurfacing.[1,2,3] More recent studies have shown that remission rates following both fully ablative and deep fractional ablative lasers are on par with 5-fluorouracil and in most cases inferior to photodynamic therapy and in the order of 44-80%.[4,5,6] The question arises: are ablative lasers still relevant? Yes, for the treatment of other aspects of solar damage, namely in the management of solar elastosis and deep rhytides, fully ablative lasers do offer excellent aesthetic outcomes, however superficial non-ablative wavelengths have been shown to have similar clearances for solar keratosis.

The 1927 nm thulium wavelength is non-ablative, meaning it preserves the stratum corneum. Common on-label densities range from 3-70%. The chromophore for this wavelength is water, however it has 10 times lower affinity for this target compared to ablative lasers. Compared to ablative lasers the depth of penetration is over twenty times less - typically 150 to 250 microns for 1927 nm thulium, compared to 4,000 microns for short pulse CO_2 lasers. Hence the histological level of laser induced apoptotic changes from 1927 nm thulium are confined to the epidermis and the upper papillary dermis (Figure 1).

The first report of non-ablative fractional lasers for the treatment of solar keratosis was in 2013. Weiss et al. showed promising results in 24 participants with facial solar keratoses. At 1-, 3-, and 6-month follow-up, participants exhibited 91.3%, 87.3%, and 86.6% reduction in lesion counts, respectively, with on-label laser densities of up to 70% with four treatments.[7]

Our group has demonstrated that super dense 1927 nm thulium with high densities of 92-94% adds a mere 36 to 48 hours downtime compared to a maximum on-label density of 70%. Solar keratosis clearance rates of up to 85% have been sustained for 6 months using this protocol. Additionally, using high power settings and super densities, the stratum corneum is still preserved (Figure 1). With these parameters, 1927 nm thulium still remains non-ablative with laser induced changes confined to the epidermis and upper papillary dermis. Preservation of the stratum corneum maintains skin barrier function. This reduces potential side effects such as infection, poor healing and subsequent scarring. It also markedly accelerates healing.

All field cancerization treatments are associated with recurrence of solar keratosis as ultraviolet (UV)-induced mutations occur within the epidermis and in the epithelium of follicular units. Hence the rate limiting factor that determines sustained efficacy may not be the complete destruction of the epidermal layer, but the burden of dysplasia in deeper adnexal units. These structures are located much deeper compared to the safe depth profile of even the powerful ablative lasers.

Over the past decade we have realised that deeper ablation does not always mean better clearance of

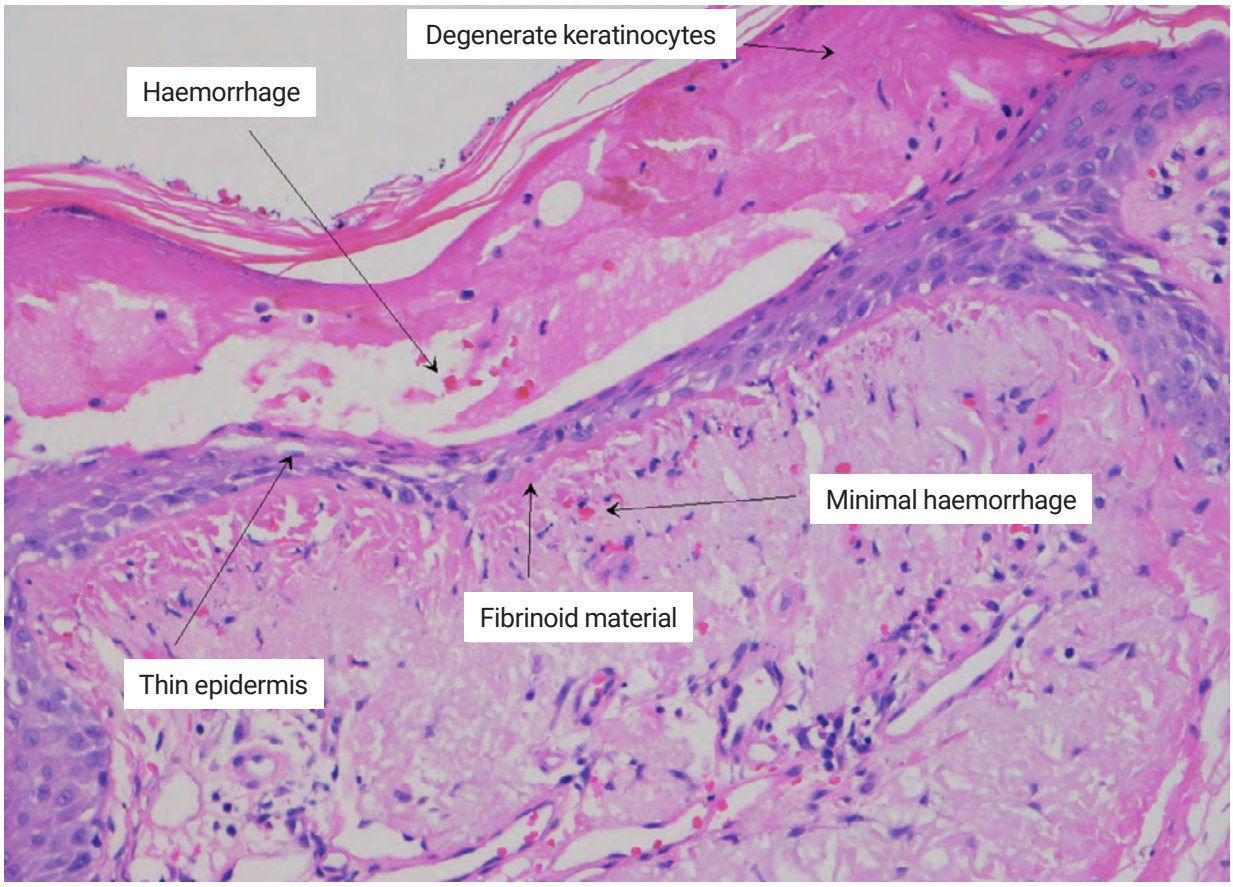

Figure 1. Histology of 1927 nm thulium 20 mJ, density coverage of 92%.

solar keratosis. We still do not fully understand why superficial non-ablative wavelengths, in particular 1927 nm thulium, consistently deliver superior outcomes out of proportion to the somewhat banal nature of histology. A possible theory is that this wavelength induces a cytokine response of adjacent keratinocytes that are undergoing involution, in turn causing an as yet undefined apoptotic cascade (the bystander effect). This cytokine flow on effect may also affect adnexal structures located deep within the reticular dermis, indirectly causing apoptosis of deeper dysplasia.

Though the chromophore of water has been studied extensively, this wavelength may have additional unknown targets, akin to 'carpet bombing' or non-selective photothermolysis. Clinicians have recognised that this wavelength improves skin quality beyond the targeted chromophore. An example is erythema and dermal remodeling. Are ectatic vessels in the papillary dermis commonly encountered in sun damaged secondary chromophores for this wavelength? How do we explain profound dermal remodeling when histology is so superficial?

As companies move to develop newer non-ablative wavelengths in addition to hybrid lasers (combining two or more wavelengths in the one device) we can look forward to novel treatments for solar keratoses in the next decade.

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How to Achieve the Best Cosmetic Outcome Treating Actinic Keratoses

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OUTLINE: Actinic keratoses (AK) represent epidermal hyperplasia with cellular atypia that result in areas of chronic ultraviolet exposure. They are often considered premalignant and thus warrant treatment. The lesions often occur in multiple individual lesions and larger plaques, which need to be treated via field therapy. They can be classified into three grades of differing thickness which then influences treatment choice. Thicker lesions warrant destructive treatment. The most common destructive option is cryosurgery. Thinner lesions can be treated via non-destructive methods applied to a field of sun-damaged skin. These treatment options include 5-fluorouracil, imiquimod, photodynamic therapy, chemical peels, diclofenac, keratolytics and emollients. These treatment options vary in their efficacy, treatment duration and side effect profile. There is also a role for maintenance therapy in the form of emollients in between reviews in the dermatology office to help reduce the number and thickness of AK. Ultimately, AK reflect a chronic process that require repeated treatment. Therefore, we require options for treating large areas of damaged skin that also provide an acceptable cosmetic result.

KEYWORDS: actinic keratosis, cryosurgery, 5-fluorouracil, imiquimod, photodynamic therapy

Farrell J, Rosen R. How to Achieve the Best Cosmetic Outcome Treating Actinic Keratoses. Opin Prog Cosmet Dermatol 2021;1(3):50-57.

Introduction

Actinic keratoses (AK) represent epidermal hyperplasia with cellular atypia that develops in areas with chronic ultraviolet exposure.[1,2] Many of the features of atypia are present within squamous cell carcinomas (SCC), which supports the classification of AK as a premalignant process. Notably, the atypia is less than full thickness, at which point it is reclassified as an SCC *in situ*.[1,2] AK classically develop as rough, scaly lesions. They may be associated with discomfort, although tenderness associated with the lesion is suggestive of a full-thickness lesion.[1] Diagnosis is made clinically, although any suspicion of an invasive SCC should prompt a biopsy for histopathological confirmation.

Histological variants of AK have been described, including hypertrophic, Bowenoid, lichenoid, acantholytic and pigmented.[2] They can be clinically graded on a three-point scale: grade I lesions have brawny scale, grade II lesions are spiky, while grade III lesions are hypertrophic, hyperkeratotic lesions.[2] This is a consideration when choosing treatment modality.

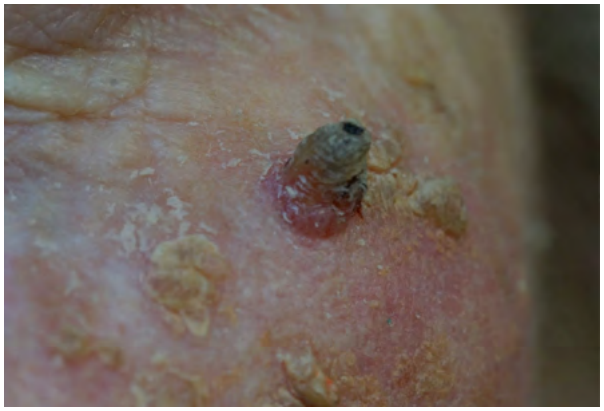

Figure 1. *Cutaneous horn with SCC in situ that requires destructive therapy*

AK often present after several decades of sun exposure, and thus commonly occur on the head, ears, neck and arms in lighter skin phototypes.[1,2] In Australia, 45% of the population over the age of 40 has on average eight AK, with men more commonly affected than women.[3] Other risk factors include chronic immunosuppression such as with organ transplantation, long-term treatment for inflammatory bowel and rheumatological disease, exposure to arsenic and sunbed use.[2]

AK can be persistent or spontaneously involute, however untreated lesions have a risk of progressing into keratinocyte cancers (Figure 1).[1,2] The risk of progression has been estimated to range from less than 0.1% to as high as 20%, although the greater the density of the lesions the higher the risk.[1,3] Although potentially low, this risk is the rationale behind treatment, which has been shown to be associated with a lower incidence of skin cancer.[2,4] AK can spontaneously regress, with the rate likely 33% with quoted rates in the literature between 15% and 70% per year, although these have a high recurrence rate of as much as 50% within the first year after spontaneous regression.[1,2,3] Overall, patients with more than 10 AK have a 14% risk of developing an SCC within 5 years.[3]

AK sometimes occur as diffuse plaques within an anatomic site that has had prolonged ultraviolet light exposure. Although individual treatment is most common, there is a desire for field treatment to cover all lesions quickly and simply. Other treatment considerations include anatomic site, efficacy, tolerability, and cosmetic appearance post treatment. Removal of keratoses may reveal invasive tumours.[2]

Treatment options include destructive therapy (cryosurgery, curettage and cautery, and excision), field therapies (photodynamic therapy [PDT], 5-fluorouracil [5-FU], imiquimod, diclofenac, chemical peels, keratolytics and retinoids), systemic therapies, radiotherapy, and emerging therapies. Treatment comparisons, advantages and disadvantages of treatment options and treatment recommendations are shown in Tables 1-3.

Destructive therapy

Destructive therapies include cryosurgery, curettage and cautery, and excision. These are best suited for hypertrophic grade III lesions or lesions that are resistant to treatment (Figures 2 and 3). They are lesion-specific treatments, with the benefit that they are completed at consultation time and patients need only comply with post-procedural care. The benefit of curettage and excision is histopathological confirmation of diagnosis. These modalities have the disadvantages of being unable to treat large numbers of AK concurrently, increased clinician time, and potential adverse events (infection, haemorrhage, scarring, pain).[2]

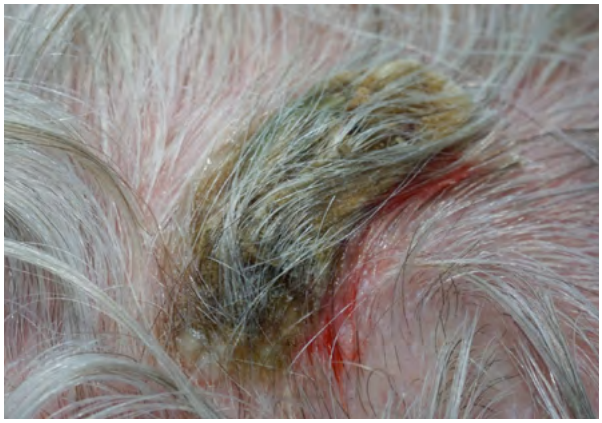

Figure 2. *Cutaneous horn on scalp that requires destructive therapy*

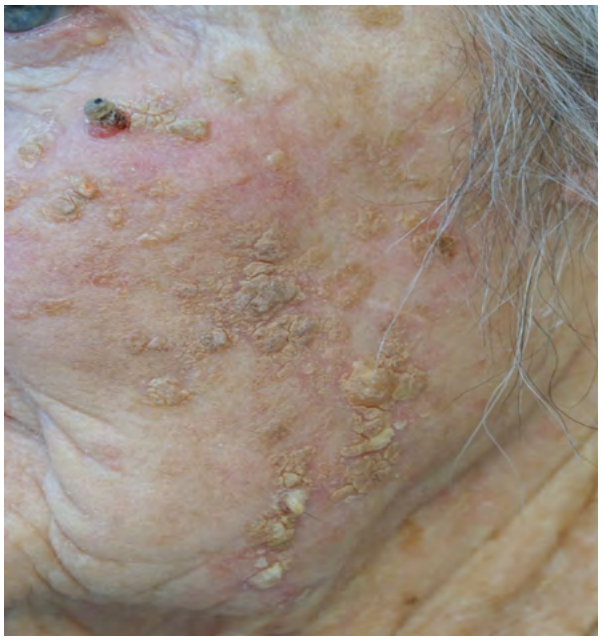

Figure 3. *Grade II and III lesions that require destructive therapy*

Cryosurgery

Cryosurgery is commonly considered the standard of care. It is a long-standing and effective treatment, which can be applied during the consultation with the dermatologist. Usually, liquid nitrogen spray is used (cotton buds do not work). The temperature of liquid nitrogen is -196°C, and it lowers the skin temperature to -60°C. Common side effects include blistering, oedema, crusting, depigmentation and pain.[2] These side effects may lead patients to prefer alternative treatments.[2]

It is a taught technique, and there are large variations in cosmetic results with scarring and permanent depigmentation (Figure 4), which reflect freeze time. A 10 second freeze can clear 85% of AK but has significant rates of hypopigmentation (54.8%).[5] Shorter freeze times allow for good cosmesis in as many as 94% of patients,[6] although there is evidence for an

improved cosmetic result with alternative therapy.[7] Slow healing can be a problem especially below the knee in elderly patients.[2] Overall, a dose of less than 10 seconds is usually sufficient to treat AK, however there remains risk of undesirable side effects.[2] Depigmentation is a concern, especially on the upper lip and decolletage in women.

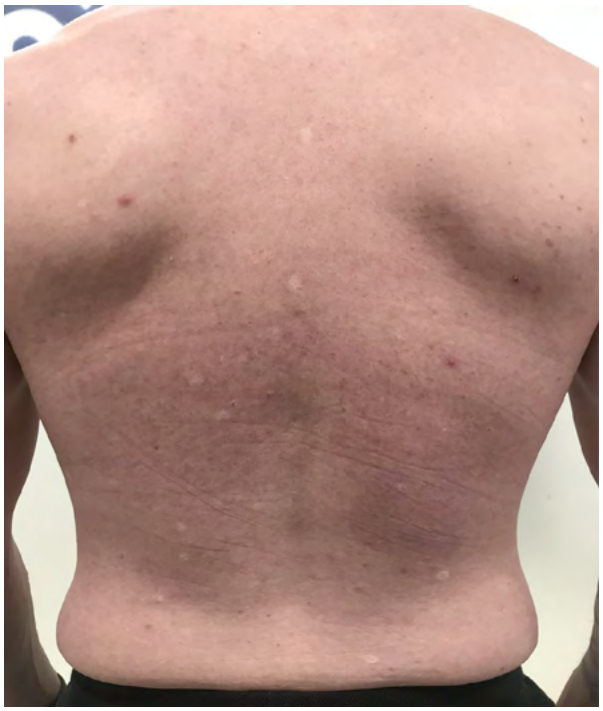

Figure 4. *Depigmentation post cryosurgery*

Surgery, curettage and cautery

There are no trials of surgery for AK.[2] Logically, surgical excision should provide focal effective treatment of a lesion. It may also provide advantage in lesions with follicular involvement.[8] It supplies histopathological confirmation of diagnosis where there is diagnostic uncertainty, however a biopsy is preferable if the diagnosis is unclear.

Curettage and cautery is good for persistent grade III lesions. However, it has the issues of scarring, depigmentation and post-operative wound care. Furthermore, 28% of patients develop recurrence after treatment.[3]

Field therapy

Field therapies have been developed in the last few decades. They have the benefit of treating keratinocyte change in a contiguous area (Figure 5) and reduce the risk of developing new AK, as well as limiting recurrence.[1,2,8] They also have benefit in treating lesions with ill-defined clinical borders.[1,8]

However, the patient-administered options can trigger more widespread local skin reactions that can affect compliance.[8] They may also be less-suited to treating hypertrophic lesions or lesions with follicular involvement.[8] It is therefore best for medical personnel to treat thicker grade II-III lesions.

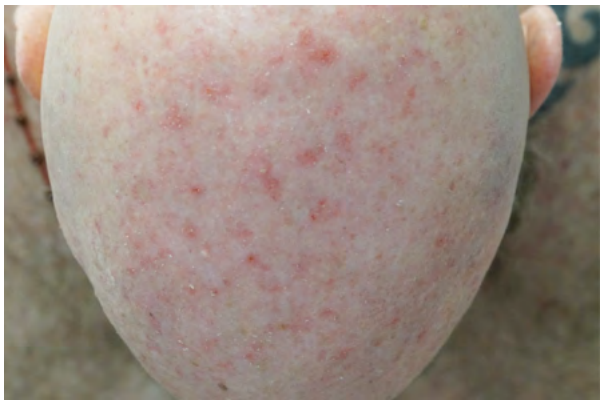

Figure 5. *Widespread AKs requiring field therapy*

5-Fluorouracil

5-FU is the work-horse of treatment options. It has been available in Australia since 1991. It is a topical cream that inhibits thymidylate synthetase and therefore DNA synthesis.[2,8] Although highly effective, it has significant side effects of pain, erythema, longer treatment time, crusting and erosions (Figure 6).[8] These can be managed through emollients, a weak steroid, a reduction in the frequency of application or a short break in therapy.[2,8] It is important to manage patient expectations to improve compliance with treatment, as the primary reason for discontinuation of treatment is local irritation.[1]

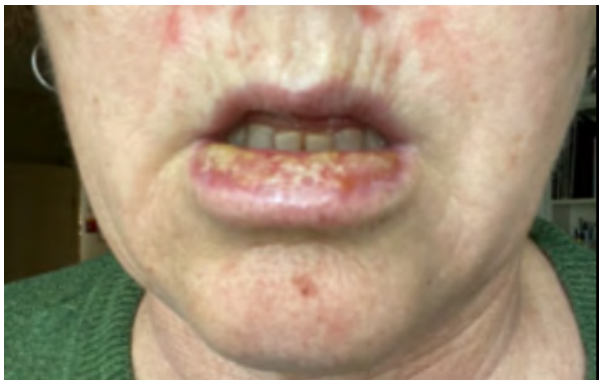

Figure 6. *Erythema and crusting due to 5-FU treatment of actinic cheilitis*

The on-label treatment course is twice daily application for 4 weeks,[2] which can provide a benefit for longer than two years.[9] Side effects require one month to settle. However, less frequent initial use may allow titration of frequency of application to reaction. This use is off-label

however and may not have the same efficacy. Care should be taken when treating areas with poor healing, such as the lower leg.[2]

5-FU most commonly comes in a 5% formulation; however, it is also available in more dilute formulations. These have the benefit of reduced irritation that quickly resolves post treatment,[10] although they may have reduced efficacy.[11] 5-FU can also be prescribed as a formulation with 10% salicylic acid. This preparation may have higher efficacy, especially when treating hyperkeratotic lesions.[2]

Overall, a recent Dutch study published in the *New England Journal of Medicine* found that 5-FU is a superior treatment option for AK at 12 months' follow up post treatment compared to imiquimod, 5-methyl aminolevulinate (MAL)-PDT, and the now discontinued ingenol mebutate.[11] Importantly, the comparative efficacy is found without regard for the grade of AK.[11] Despite this, the authors of this study identified that only 90.3% of patients had good-to-excellent cosmetic outcome, compared to 96.6% of MAL-PDT patients and 89.7% of imiquimod patients.[11] 5-FU also has variable efficacy in treating Bowen's disease when this is a possible alternative diagnosis.[12] Overall, although low cost, 5-FU has considerably more side effects.

Imiquimod

Imiquimod, available in Australia since 1998, works by upregulating toll-like receptor 7 to trigger localised inflammation.[8] It thus has side effects of localised skin irritation in up to 98% of patients, but may also cause influenza-like symptoms in up to 10% of patients.[1,2] Skin irritation includes severe erythema (30%), scabbing (30%), and erosions (10%)[2] (Figure 7). It can also cause erosions and scar formation, especially on the chest. Influenza-like symptoms are more likely when treating superficial basal cell carcinoma (BCC) or with more frequent applications.[2] Clinical response is often in proportion to side effects, and thus patients who terminate their treatment early due to severe side effects may still achieve a good clinical result.[2] Around 2% of patients may also develop infections.[1]

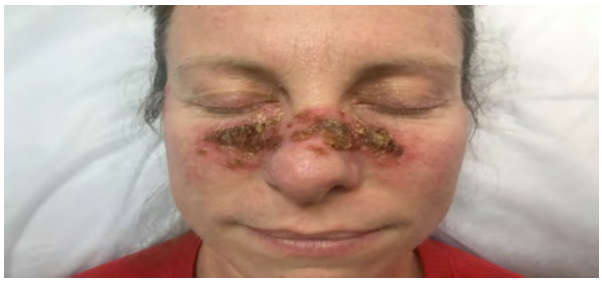

Figure 7. Imiquimod reaction. This figure illustrates that inflammatory response is unpredictable and greater than the size of the treatment area

Imiquimod is applied nightly, and washed off in the morning 8 hours later. The recommended application regimen of imiquimod is 2-3 times per week for 4 weeks, which can be extended for a total of 8 weeks if needed.[2] Complete clearance with this regimen after 4 weeks is 26.8%, and after 8 weeks is 53.7%.[13] There are improved clearance rates with a greater number of applications: 30% clearance of AK with 9-24 doses of imiquimod, and greater than 40% clearance with 32-56 doses.[1,2]

Unfortunately, as many as one third of patients will discontinue treatment due to side effects on longer regimens.[1] Standard concentration of imiquimod is 5%, and lower concentrations of imiquimod of 3.75% and 2.5% are better tolerated whilst still maintaining effectiveness.[1,2] However, there is likely a greater recurrence rate of AK with these lower concentrations.[1,2] Recurrence rate after 12 months with a standard 5% strength may be as low as 24%,[2] compared to 40% with weaker formulations.[2]

Imiquimod generally provides a good cosmetic outcome; notably, a minority of patients may develop dyschromia, scarring and skin atrophy especially when used on the chest and face.[13] These severe side effects need to be weighed against the benign nature of the problem.

Photodynamic therapy

PDT, available in Australia since 2003, is an elegant and finessed treatment whereby a photosensitising compound is applied to the target area several hours prior to application of a light source. There are two widely used sensitising agents: 5-aminolevulinic acid (ALA) and its methyl ester, MAL.[14] Metvix is the standard MAL preparation. It is taken up selectively by malignant cells, resulting in higher intracellular protoporphyrin IX. Activation by light generates reactive oxygen species and thus cell death.[15] Red spectrum light sources likely provide higher response rates with shorter illumination times, although other spectrum light sources are used.[2]

The treatment area is gently curetted prior to application of the photosensitising compound to increase absorption and then occluded. Longer incubation times correlate with higher complete clearance: 0.5 hours incubation equates to 51% of lesion complete clearance whereas 4-hour incubation equates to 86% complete clearance.[16] A standard incubation period is 3 hours.[1] Often AK only require one treatment session, but more hypertrophic lesions can require a second treatment 1-2 weeks later. This provides 90% clearance at 3 and 6 months.[17]

PDT is a good treatment option, with improved compliance compared to out-of-office treatment.[1] A network meta-analysis looking at treatment options for AK available in Europe found that the best treatment option is ALA-PDT, which had complete clearance rates of 77% at 12 weeks post treatment.[18] As noted above, there are higher rates of 90% complete clearance with two treatment sessions 1-2 weeks apart.[17] PDT appears to work best for the face and scalp,[2] although it is a safe option in areas with poor healing such as the lower leg in older patients.[2]

The side effects of PDT include skin irritation, variable pain and erythema,[1,2] although these are milder than in other treatments. The side effects correlate with incubation time and may represent increased efficacy of treatment.[16] An alternative method is daylight PDT, where the energy source is sunlight rather than artificial. MAL is applied to the skin without occlusion for 30 minutes, before 2 hours of exposure to daylight.[2] This may have similar efficacy but reduced pain at time of treatment.[1] Daylight PDT is best suited for grade I and II AK rather than hypertrophic lesions.

PDT has a good cosmetic result (Figure 8), and also has the benefit of clearing pigmentation and improving photoageing. It can also be used to treat Bowen's disease and BCC if this is a differential diagnosis.

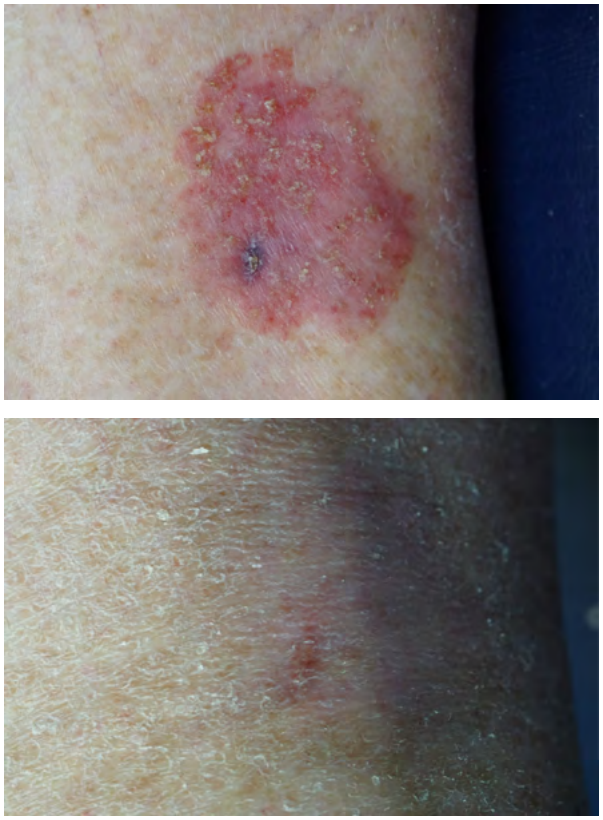

Figure 8. PDT to the ankle for Bowen's disease. Before treatment (top) and after treatment (bottom)

Chemical peels

Chemical peels have long been used to treat AK although less often more recently.[15] They provide chemical ablation of skin, followed by regeneration of the epidermis and superficial dermis.[15] The depth of ablation can be controlled via chemical choice and concentration.[2] Superficial peels induce epidermal injury whilst medium-depth peels penetrate into or through the papillary dermis.[19] AK can be treated by either, but are likely to be more completely treated with medium-depth peels.

Glycolic acid is a superficial agent used in chemical peels. One study compared weekly application of 70% glycolic acid for 2 minutes compared to 5-FU over 8 weeks.[20] This cleared only 20% of AK at 6 months.[20] Thus, glycolic acid and other superficial peels including salicylic acid are perhaps best used for the indications of mild acne, and epidermal and mixed melasma.[19]

Trichloroacetic acid (TCA) is a common agent used for medium-depth peels, and likely has the most evidence of the chemical peels regarding efficacy.[14,15] Despite this, it is possibly less efficacious than other treatment options, with one study finding mean clearance rates for 35% TCA of 79% after 3 months and 49% after 12 months, compared to PDT (89% and 74%, respectively).[15] This result could be improved with the concomitant application of 0.05% or 0.025% tretinoin before and after treatment, or with the concurrent application of Jessner's solution (resorcinol, lactic acid, salicylic acid in ethanol), which facilitates deeper penetration.[14,15,21] Concurrent application with Jessner's solution may also provide sustained clearance.[21] Similarly, higher concentrations of 50% TCA have comparable clearance rates to 35% TCA, but may have better sustained clearance.[14]

Chemical peels are often well tolerated.[21] They typically cause transient erythema and discomfort for up to one week after application.[21] They have a high risk of scarring, especially when used off the face and scalp.[21] They may also cause hypopigmentation due to their non-selective ablation which can be reversible.[2,8,14] They can treat larger areas than other field treatments, however, they are often used sparingly as they have unpredictable cosmetic results.[15] However, they have a low cost and are easily used in 1-2 applications in-office.[15,21]

Diclofenac

Diclofenac is a non-steroidal anti-inflammatory medication. Its mechanism of action for AK is unclear, however it may be related to inhibition of the cyclooxygenase pathway which is responsible for inhibiting apoptosis and promoting angiogenesis.[2,8]

It is very well tolerated with far fewer intense local skin reactions than other treatments.[2] It is licensed for twice daily application for 60-90 days.[2]

The fewer side effects of diclofenac translate to reduced efficacy, however twice daily application for 60 days may clear 33% of AK whilst twice daily application for 90 days may clear 42%.[22] Recurrence is around 19% after 12 months.[2] Discontinuation from local side effects occurs in 15% of patients,[1] with the commonest side effects being pruritis (41% of patients) and a rash (40% of patients).[2] Other side effects include paraesthesia, oedema, and contact dermatitis.[8] However, diclofenac carries warnings for increased thrombotic risk and gastrointestinal bleeding.[1]

There is a role for topical therapy in between patient visits to the dermatologist to reduce AK disease burden, and diclofenac is part of the therapeutic options. Other options include keratolytics, emollients, and sunscreen.

Keratolytics and emollients

Keratolytics such as urea or salicylic acid may provide some benefit.[2] There is a role for keratolytics in between treatment sessions in the dermatologist's rooms to treat grade I-II AK, and to reduce the thickness of hypertrophic lesions to improve subsequent treatment efficacy. Commonly used keratolytics are urea 20% and salicylic acid 4% formulations. Treatment of milder AK may also reduce the frequency of attendance at dermatologists' rooms.

Emollients have little evidence aside from acting as the placebo arm in clinical trials. It has been reported that up to 14.1% of AK are cleared with emollients applied 3 times per week for 8 weeks.[13]

Sunscreen is important in the prevention of skin cancer and has a combined emollient and photoprotective effect.[2] It has been associated with a resolution in 25% of AK over 12 months,[3,17] as well as a subsequent reduction in the number of SCC.[2,17] Daily application of sunscreen appears to have a greater protective effect than discretionary application.[2] It thus has an important position in AK maintenance therapy.

Topical retinoids

There is not a lot of evidence for topical retinoids in the treatment of AK. However, they do provide improvement in wrinkles and lentigines.[2] Their use tends to be sustained, rather than limited to one treatment course. Formulations include adapalene 0.3%, tretinoin 0.1%, tretinoin 0.05%, and isotretinoin 0.1%. There is some evidence for adapalene 0.3% providing greater benefit than adapalene 0.1% after 9 months of application.[2]

Radiotherapy

Radiotherapy is a treatment modality in which the target tissue is exposed to ionising radiation, which damages DNA. Malignant cells have poor DNA repair capacity. Therefore, radiotherapy can destroy malignant tissue and preserve normal tissue.[17] Radiotherapy has advantages of very good functional and cosmetic outcomes, especially where it is important to conserve tissue. However, it needs to be administered repeatedly (fractionation) and should the fractionation be too high, it exceeds the repair capacity of normal tissue causing cell death and fibrosis. This causes tissue retraction and thus poor cosmesis and function.[17]

Radiotherapy is usually considered to treat AK only in the form of salvage treatment after repeated failures of other therapies, especially for high grade lesions on the scalp.[17] It does not have a role as a first-line treatment option given the risks of poor outcomes. It also has the risks of radio-necrotic ulcers and fistulae should re-treatment be required in the future.

Tirbanibulin

Topical tirbanibulin 1% has been recently approved by the US FDA for treatment of AK on the face and scalp based on phase III trials.[1] It is an ointment that is applied daily for 5 consecutive days.[23] It completely clears AK in 44-54% of patients with a recurrence rate of 47% after 12 months.[23] Side effects are classed as mild-to-moderate, with 91% of patients experiencing erythema and 82% experiencing scaling.[23] No patients withdrew from treatment in the phase II trials due erythema and scaling.[23] It thus represents an emerging option for treatment although is not currently available in Australia.

Conclusion

Treatment of AK needs to take into account the dynamic aspect of AK as a sign of a chronic evolution of DNA damage which requires repeated treatment. A treatment option that is well-tolerated but also provides acceptable clearance and cosmetic results is therefore important. It also needs to be able to treat fields of damaged skin. When treating AK, clinicians should note potential for progression to SCC. There are no data on the benefit of follow up,[2] although the presence of greater than 10 AKs is an indicator of higher risk for keratinocyte cancers[2] with a 14% risk of an SCC within 5 years.[3] Patients should therefore be followed up within five years, especially in cases where treatment is likely to require evaluation and adjustment. Maintenance treatment in the form of emollients with keratolytics such as urea or sunscreen is useful and should be encouraged.

Table 1. *Comparison of treatment options*

Treatment	Doctor	Patient	Time	Pain	Scars	Recurrence	Cosmesis
Cryosurgery	Y		10s	Y	Y	15%	Depigmentation
C+C	Y		One session		Y	28%	Depigmentation
Surgery	Y		One session		Y	0%	Depigmentation
5-FU		Y	2x daily for 4 weeks	Y	Y	25%	Significant erythema
Imiquimod		Y	2-3x/week for 4 weeks	Y	Y (on chest)	24%	Dyschromia, depigmentation
PDT	Y		2 sessions, 2 weeks apart	Y		10%	Excellent

5-FU, 5-fluorouracil; C+C, curettage and cautery; PDT, photodynamic therapy

Table 2. *Advantages and disadvantages of treatment options*

Treatment	Advantages	Disadvantages
Cryosurgery	Low cost, quick, occurs in rooms	Pain, cosmesis, treatment of single lesions
5-FU	Low cost, field therapy	Significant side effects, poor cosmesis for several months
5% Imiquimod	Low cost	Variable inflammatory reaction
PDT	Occurs in rooms in 1-2 treatments	Requires specialised equipment, high cost
Diclofenac	Low cost	Relatively low efficacy, long treatment course
Chemical peels	1-2 treatments in rooms, improves photoageing	Unpredictable cosmetic results, low efficacy

5-FU, 5-fluorouracil; PDT, photodynamic therapy

Table 3. *Treatment recommendations*

Treatment	Treatment indication	Cosmesis
Cryosurgery	Lesions of all grades	Hypopigmentation and depigmentation especially on the face and decolletage, blistering, pain and infection
5-FU	Multiple grade I-II lesions	Erythema, down-time for recovery
5% Imiquimod	Multiple grade I-II lesions, can also treat Bowen's disease	Dyschromia, scarring, atrophy, infection, uncontrolled inflammatory reaction, down-time for recovery
PDT	Multiple grade I-II lesions as well as Bowen's disease, with 2 sessions of PDT for persistent lesions	Excellent cosmesis
Diclofenac, 90 days	Diffuse grade I lesions	Not significant
Chemical peels, TCA	Multiple grade I-III lesions	Scarring, dyschromia

5-FU, 5-fluorouracil; PDT, photodynamic therapy; TCA, trichloroacetic acid

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