Research Review Speaker Series™

Patient centric topical treatment of actinic (solar) keratosis

Dr Franz Strydom

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Dr Franz Strydom is the founder of Skinspots skin cancer clinic which provides general practice based skin cancer care including detection, prevention and treatment. Dr Strydom was part of the team that developed the minor surgery skin cancer project for the New Zealand Ministry of Health in the Bay of Plenty region and is credentialed by the District Health Board to provide basic to advanced level of care for patients with skin cancer. The clinic is also an Affiliated Provider to Southern Cross Health Society for selected skin services. Dr Strydom was the first New Zealand doctor to receive a fellowship from Skin Cancer College Australasia.

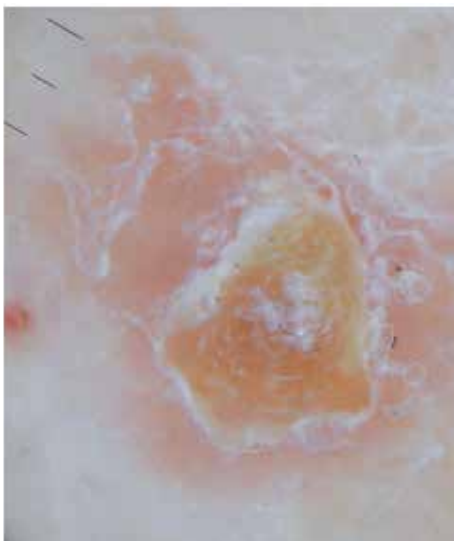
Abbreviations used in this review:

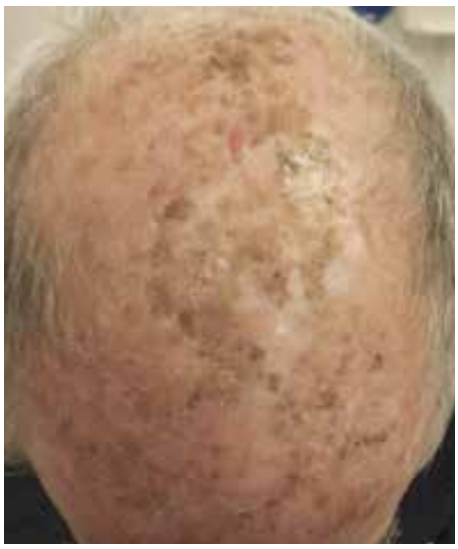
5-FU	=	5-fluorouracil
AK	=	actinic (solar) keratosis
BCC	=	basal cell carcinoma
cSCC	=	cutaneous squamous cell carcinoma
PDT	=	photodynamic therapy
SCC	=	squamous cell carcinoma

Welcome to this review of a presentation by Dr Franz Strydom at UQ HealthCert Skin Cancer Conference 2014 held in Noosa, QLD. Dr Strydom, a GP with a special interest in skin cancer management, discussed improving treatment of actinic (solar) keratosis (AK) and early non-melanoma skin cancer, with a review and introduction of patient centric group clinics.

Actinic (solar) keratoses (AKs) represent early lesions on a continuum towards squamous cell carcinoma (SCC) and occur in areas of sun exposure (see Figure 1). The likelihood of progression of an individual AK to SCC is low, with estimated annual rate of progression ranging from 0.03–20%.[1] Within one year, about 20–30% of AKs will spontaneously resolve while 15–53% will recur. It is important to note that approximately 60% of cutaneous SCCs (cSCC) arise from pre-existing AKs.[1]

Figure 1. Actinic keratosis dermatoscopic and large area of actinic skin damage





The common clinical, histologic and molecular features of human cutaneous neoplasia are shown in Table 1. It can be seen that as skin progresses from normal to metastatic cSCC, the number and range of mutations increases. AKs are a marker of chronic sun damage and other skin cancers – patients with AKs have an increased risk for skin cancer at local and other sites. In general, AKs should be treated, primarily because it is not known which lesions will progress to SCC. In a poll taken on the 70 delegates in the audience, 86% said they would treat AKs, 13% said whether or not to treat depends on a number of factors, and 1% stated they would not treat AKs.

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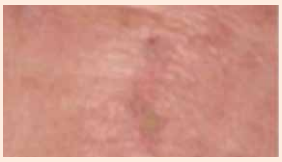
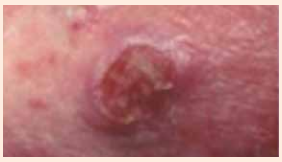
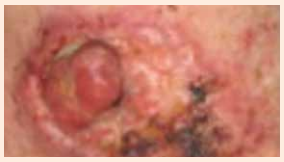
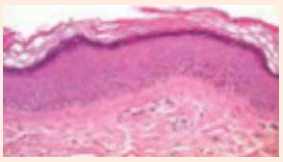
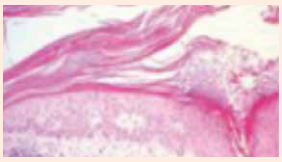
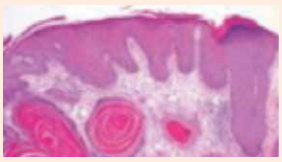
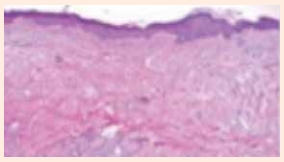
Table 1. Clinical, histologic and molecular comparison of AK, cSCC, and metastatic cSCC (modified from Ratushny et al. 2012)

	Normal skin	AK	cSCC	Metastatic cSCC
Clinical description		 Scaly skin coloured/pink macule or papule	 Persistent firm or scaly papule or red nodule which may spontaneously bleed	 Multiple nodular lesions in skin or internal organs
Histopathology	 Well-defined stratum basalis, spinosum, and granulosum with orthokerototic scale	 Enlarged, atypical keratinocytes confined to the epidermis with parakerototic scale	 Enlarged, atypical keratinocytes invading the dermis	 Enlarged, atypical keratinocytes in the dermis, lymph nodes, or internal organs, typically with no epidermal connection
Increased signalling (activation, overexpression, or amplification)		Ras Fyn/SFKs bcl-2	Ras Fyn/SFKs c-myc bcl-2 STAT-3 ß-1 intergrin MMP	In addition to cSCC alterations: VEGF (ras) MMP2 MMP7 MMP12 (ras)
Decreased signalling (deactivation, transcriptional or translational repression, or gene deletion)		p53 Srcasm	p53 Srcasm Notch (p53) PKC δ E-cadherin	In addition to cSCC alterations: P-cadherin
Genomic changes		Genomic instability with few chromosomal alterations	Increased genomic instability resulting in chromosomal translocations, isochromosomes, gene deletions, and amplifications	

Treatment options

Treatment should be considered for visible lesions and also for those that are not clinically obvious. The idea of field cancerization[2] was conceived by Slaughter almost a decade prior to introducing the term in 1953. In an earlier publication he stated that 'cancer does not arise as an isolated cellular phenomenon, but rather as an anaplastic tendency involving many cells at once'. Dr Strydom considers Slaughter's approach in the treatment of AK. Treatment options include:

- Lesion-directed destructive treatments
  - Cryotherapy – most commonly utilized technique with cure rates ranging from 39–83% in a prospective study[3]
  - Curettage and shave excision (very little data available)
- Field treatments
  - Photodynamic therapy (PDT) – cure rates of 59–91% at 3 months in four randomised trials[4]
  - Topical 5-fluorouracil (5-FU; Efudix® cream) – two systematic reviews found a 50% overall efficacy rate of 5-FU for 100% clearance of AKs[5,6]
  - Imiquimod (Aldara™ cream) – imiquimod 5% cream resulted in complete resolution of AKs in 50% of patients compared to 5% with the control vehicle in a meta-analysis of five randomised trials[7]
  - Ingenol mebutate (Picato® gel)* – complete clearance of AKs was achieved in 42% of patients when treating the face and scalp in two randomised trials[8]
  - Diclofenac (Solaraze® gel) – complete resolution of AKs in 40% of patients in a meta-analysis of three randomised trials[9]

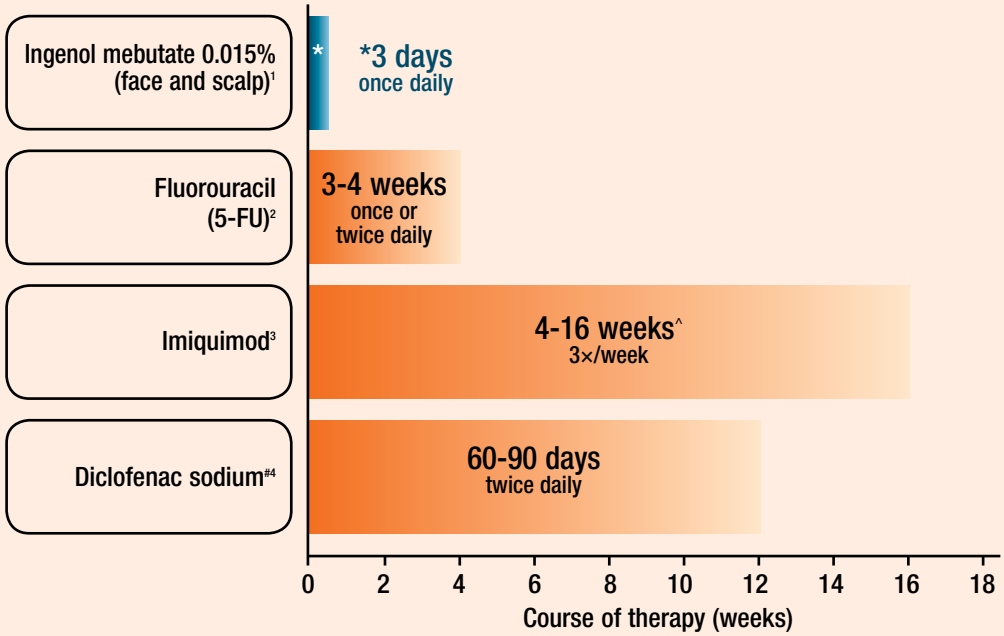
When conference delegates were polled on how they treat AKs, 15% said they use lesion-directed destructive treatments, 11% said they use topical medical treatments and 75% said they use both types of therapy (some delegates chose more than one answer). Dr Strydom treats obvious cancers and AKs with lesion-directed destructive therapy. Regarding other lesions that are not quite so obvious Dr Strydom removes the keratotic scale then treats the whole area* with topical therapy. He says this method also treats subclinical lesions that are not detected by visual inspection or palpation.

Delegates were presented with three case reports including photos and were then polled on how they would treat each patient. In the first two patients with multiple areas of AKs, surgery was the most popular first-line treatment, followed by topical therapy. In Dr Strydom's view, it would be very difficult to determine the margins of each lesion for surgery in patients with multiple cancers, so he would use topical therapy first then adjuvant surgery. For the third case, a patient with no previous skin cancer and some areas of AK, topical therapies were the most popular. The majority of delegates would treat the full face in all three cases.*

Low patient adherence

The advantage of topical therapies versus surgery is that they are non-invasive, effective against subclinical lesions and can be self-administered. However, patient adherence is generally low. This is because of the high frequency of adverse events (e.g. skin irritation, erosions and ulcerations) and the long duration of treatment required for some topical agents. Dr Strydom highlighted this with his experience of patients undergoing topical 5-FU therapy. Compliance is poor and complications are numerous. Furthermore, patients report the therapy to be painful and unsupervised and feel that they are unsupported. The duration of therapy required for a number of different topical agents is shown in Figure 2.

Figure 2. Actinic (solar) keratosis therapy duration on the face and scalp



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2. Australian Efudix® Product Information. 01 May 2013. New Zealand Efudix® Data Sheet. 19 April 2013.
3. Australian Aldara™ Product Information. 24 June 2014. New Zealand Aldara™ Data Sheet. 12 June 2014.
4. Australian Solaraze® Gel Product Information. 19 January 2015.

^ 4-12 weeks for New Zealand
# Diclofenac sodium gel is not marketed in New Zealand

Picato® (ingenol mebutate) gel 0.015%, 0.05%

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Bay of Plenty
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- MoleMap's Picato® Application Clinic 0800 665 362
- Mount Medical Centre 07 575 3073

Christchurch
- Christchurch Skin Cancer Clinic 0800 547 678

North Canterbury
- Amuri Community Health Centre 03 315 6328

Queenstown / Invercargill
- Skin Institute 03 442 2255

Wellington
- NZ Dermatology & Skin Cancer Centre 04 380 0125
- Upper Health Centre 04 920 1800

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Improving outcomes with group therapy

Dr Strydom treats his patients in group clinics. These clinics are well supported and appreciated by patients and have fostered peer support between them. The clinics also allow for better monitoring of and quick response to complications. Dr Strydom presented a review of 76 patients treated in a clinical group setting with ingenol mebutate (see Table 2). Patients were asked a series of questions reflecting compliance and experience from their own viewpoint. Response rate for the questionnaire was 95%.

Table 2. Survey of 76 patients treated in a group setting with ingenol mebutate

Question	(%)
Has the treatment improved the way your skin looks to you?	
• Yes	86
• No	14
Which of the following did you find to be the most distressing thing about using Picato® gel	
• Appearance	59
• Pain	46
• Anxiety	12
How important was the group based treatment to you?	
• Unimportant	10
• Low importance	1
• Neutral	20
• Important	38
• Very important	28
How important was regular review by health professionals to you?	
• Important	30
• Very important	70

Note: some patients chose more than one answer or did not answer all questions

Dr Strydom has started treating patients with ingenol mebutate which has revolutionised his clinics because of the three day treatment period versus longer for 5-FU. Ingenol mebutate is painted on with a brush[1] in his clinic – he has found that when clinic nurses administer repeated applications by finger their skin deteriorates, so suggests wearing gloves or administering by brush. He treats the whole face with 3 single unit tubes of 0.015% for 3 consecutive days and has found no systemic adverse events to date. Figure 3 shows a patient with AK before, during (day 3) and after (2 weeks) treatment with ingenol mebutate 0.015% gel. This patient had full face therapy with very good AK clearance. At 2 weeks, one SCC and one BCC remained and were removed with surgery. Currently, nine clinics in New Zealand are offering full face group therapy with ingenol mebutate.

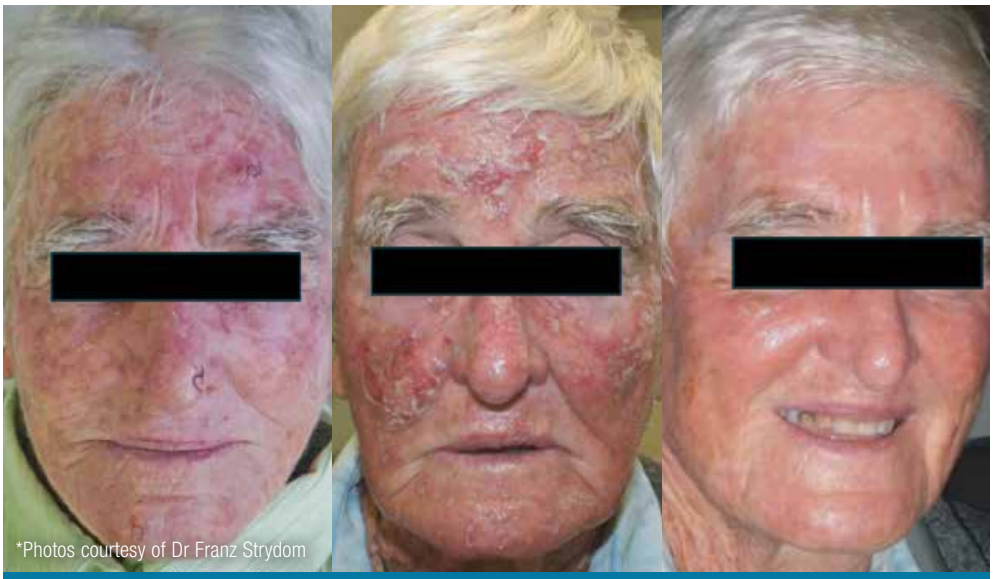
Group clinic key points

- Offering weekly group clinics
- Well supported and appreciated by patients
- Allows for better monitoring for complications
- Allows for quick response to complications
- Allows peer support between patients

Wound management

Lastly, Dr Strydom discussed management of patients with topical treatment superficial ulceration on their faces – a common problem in the patient undergoing treatment for AK. Occlusive wound cover results in up to 50% faster wound healing (epithelisation and dermal repair) and heals wounds within 2 weeks. It is associated with lower rates of infection, less pain, less scarring and better cosmetic results.[10-14] Pain is caused by a wound drying out and forming painful scabs, so if a wound is prevented from drying out by using an occlusive cover, clinicians can make a big difference to patients' comfort and adherence to therapy. By using an occlusive cover, clotting is prevented meaning a wound is healed all the way through and scarring is minimised. Dr Strydom uses Bepanthen® cream and finds it works very well as an effective occlusive cover.

Figure 3. Before, during and after topical ingenol mebutate 0.015% gel treatment



*The New Zealand and Australian Product Information state that Picato® gel should be applied to the treatment area as defined by the treating physician. Each tube contains enough gel to cover an area of approximately 25 cm^2 (e.g. 5 cm x 5 cm).

ǂ The New Zealand and Australian Product Information state that Picato® gel should be applied by fingertip. In clinical study 4 single dose tubes of Picato® gel, 0.05% was applied daily for 2 consecutive days to a 100 cm^2 area of skin for the treatment of solar keratoses. The result demonstrated no change in the safety profile compared to the safety profile of Picato® gel, 0.05% when 1 tube is applied to a 25 cm^2 area for 2 consecutive days.[15,16]

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15. New Zealand Data Sheet. Picato® gel. 19th February 2014.
16. Australian Product Information. Picato® gel. 28th August 2014.

Picato® gel, 0.015% and 0.05%, are unfunded medicines – a prescription charge will apply

PRESCRIPTION MEDICINE. PLEASE REVIEW DATA SHEET BEFORE PRESCRIBING. Minimum Data Sheet: Picato® gel. Ingenol mebutate 0.015%, ingenol mebutate 0.05%. Indication: Topical treatment of solar (actinic) keratoses in adults. Contraindications: Allergic sensitisation to ingenol mebutate or any other constituent of Picato® gel. Precautions: For external use only; not for oral, ophthalmic, vaginal or anal use. Avoid eye area. Most common local skin responses include erythema and flaking/scaling followed by crusting and swelling. Less common include vesiculation/pustulation and erosion/ulceration. Local skin responses are transient and typically occur within one day of treatment initiation and peak in intensity up to one week following completion of treatment. Local skin responses typically resolve within 2 weeks for face and scalp and within 4 weeks for body. Avoid excessive exposure of treated areas to sunlight/UV. As a precautionary measure, it is preferable to avoid use during pregnancy. Avoid infants contacting treated areas within 6 hours of application. Not indicated for children below 18 years. Adverse Effects: Adverse effects occurred in less than 10% of patients and included application site pain, pruritus, irritation, infection, periorbital oedema, headache, paraesthesia, eyelid oedema. See Precautions for local skin responses. Dosage and Administration: Solar (actinic) keratoses on the face and scalp: Picato® gel, 0.015% should be applied to the affected area once daily for 3 consecutive days. Solar (actinic) keratoses on the body: Picato® gel, 0.05% should be applied to the affected area once daily for 2 consecutive days. Picato® gel should be applied to the treatment area as defined by the treating physician. Each tube contains enough gel to cover an area of approximately 25 cm^2 (e.g. 5 cm x 5 cm). Store at 2-8°C (Refrigerate). Revised Jan 2015 based on Data sheet dated 19 Feb 2014. LNZ-14-008. Datasheet is available directly from www.medsafe.govt.nz or by calling 0800 497 456 LEO Pharma Limited, Level 31, Vero Centre, 48 Shortland Street Auckland. TAPS CH4486

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